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THE CONVERSION OF LOGANIN TO AN ANALOG OF PROSTAGLANDIN INTERMEDIATE

City University of New York PH.D. 1987

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THE CONVERSION OF LOGANIN TO AN ANALOG

OF

PROSTAGLANDIN INTERMEDIATE

by

ABDEL-FATTAH M. ARAFAT

A dissertation submitted to the graduate faculty in chemistry in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York.

1987

This manuscript has been read and accepted for the Graduate Faculty in Chemistry in satisfaction of the dissertation requirements for the degree of Doctor of Philosophy.

12/1/86
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William Frost Berkowitz
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12/2/86
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A. N.
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George Stellman

R W Franck

William Frost Berkowitz
Supervisory Committee

The City University of New York

Abstract

THE CONVERSION OF LOGANIN TO AN ANALOG

OF

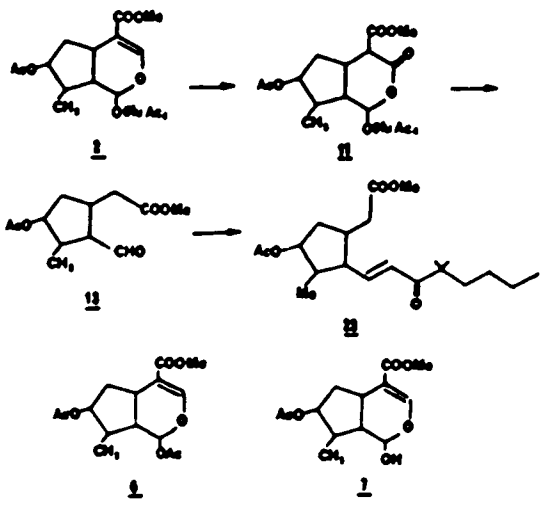
PROSTAGLANDIN INTERMEDIATE

by

Abdel-Fattah M. Arafat

Adviser: Professor William F. Berkowitz

The prostaglandin analog intermediate 23a, has been prepared from Loganin 1. The enol ether system of the pentaacetate of this iridoid 2 was oxidized to the corresponding lactone 11. Ring opening, glucose cleavage and decarboxylation of this lactone was accomplished in one pot to give the key intermediate aldehyde-ester 13, in good yield. Wadsworth-Emmons reaction of 13 gave the desired prostanoid-like trans 23 in 81% yield. The phosphonate reagent 22 was prepared in a two step reaction in 76% yield. Several other potential intermediates were also prepared from loganin in particular, compounds 6 and 7.



TO

my wife, my son and my daughter

ACKNOWLEDGEMENTS

I wish to express my sincere thanks to the members of the Queens College Chemistry Department for having made integral contributions to the completion of this wark.

In particular, I thank professor William Berkowitz for his invaluable advice, guidance and constant encouragement for the completion of this project.

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I also thank Mr. Robert Wurman and Mr. Randy Smith for their technical assistance and cooperation.

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I- INTRODUCTION

Natural phenomena have always provided chemical and biological questions for the curious. One chemical mystery, questioned avidly in recent years, concerns the activity of, and possible synthetic routes to prostaglandins. Prostaglandins are powerful, hormone-like chemicals found in human, animal and plant tissues. The possible medicinal and therapeutic value of prostaglandins has received wide attention. Drawbacks for the use of natural prostaglandins as medicines are, of course, their wide range of activities and their metabolic instability. In the past, analogs that have been studied clinically suffered from a lack of selectivity, but nowadays, a better understanding of prostaglandin structure-activity relationships and metabolism has led to more selective and better tolerated analogs .

II- Early History

In 1930, scientists discovered a relationship between the presence of semen and the contraction or relaxation of uterine muscle, provided the uterine sample was from a donor who had borne children[1]. In Sweden at this time, Goldblatt and Von Euler[2,3] noted a substance, common to sheep vesicular glands and human seminal plasma, having physiological effects similar to adrenalin, histamine and

acetylcholine[4]; namely a decrease in blood pressure and contraction of smooth muscle were demonstrated in laboratory animal tissue. Von Euler, using specific chemical inhibitors, showed this to be a new substance different from those having similar biological effects, as it was a lipid soluble acid[5,6].

Two major sources of this substance were sheep vesicular glands and human seminal plasma. Due to the anatomical sources of the substance in question, Von Euler named it " prostaglandin"[3]. Later, it was noted that prostaglandins were present in all organs, though present in less than 1% of the amount found in the prostate gland. Von Euler isolated prostaglandins from chloroform extracts of sheep vesicular gland fluids, followed by conversion of water soluble acids into barium salts, as a stable amorphous powder which could be stored. Unfortunately, the prostaglandin mixture was too complex for the technology of the times to purify further[7].

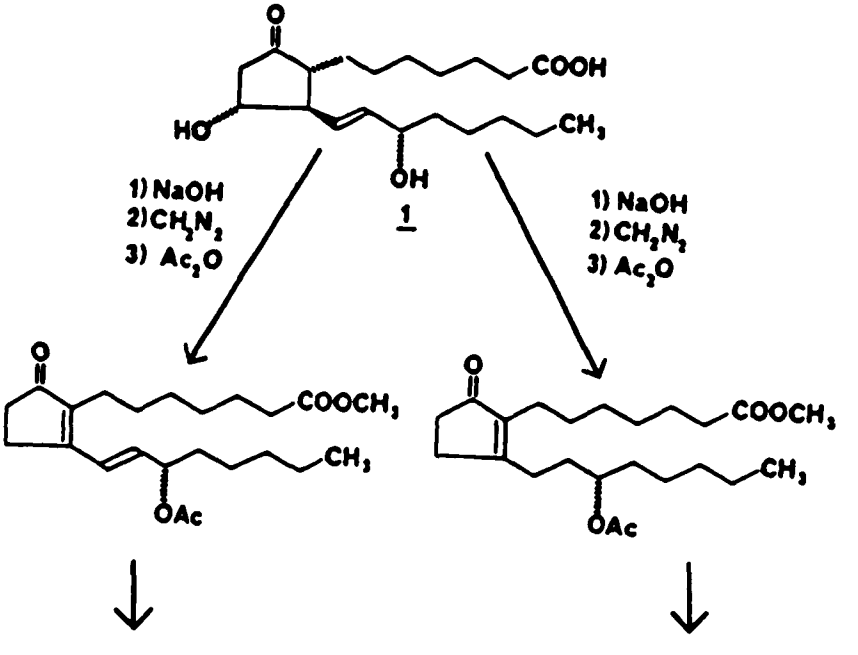
Little progress was made after Von Euler's work until the mid 1950's for a number of reasons. To begin with, there was a lack of a sufficient prostaglandin source for study. Analytical purification and separation techniques were not sophisticated enough. In addition, at this time in history, research on steroid hormones and antibiotics took major priority over other chemical research.

Nevertheless, in 1957, Bergstrom and his associaties, isolated two major compounds from chloroform extracts of sheep vesicular glands as crystalline prostaglandins[8]. Due to the biological activity expressed by a number of prostaglandins, Bergstrom postulated that a prostaglandin wasn't a specific chemical, but rather a family of related compounds with similar structural precursors[9]. Bergstrom showed that prostaglandins were twenty carbon acids differing by one unit of unsaturation between compound types [9,10]. Bergstrom also explained the ambiguous biological results expressed by Von Euler's amorphous solid. Apparently, the amorphous powder contained crystals of two different prostaglandins: PGF and PGE [11]. PGE was found to effect both intestinal muscles and blood pressure of a rabbit [11]. PGF, on the other hand, didn't effect the blood pressure of the system but contracted smooth muscle tissue[12].

Bergstrom also founded a nomenclature based on prostaglandin solubility. That is, PGE, later to become PGE_1, is ether soluble, and PGF, later to become $PGF_{1\alpha}$[13] was fosphate (in Sweden) buffer soluble. By the mid-1960's Bergstrom and co-workers isolated a series of twelve prostaglandins from human seminal plasma. Determination of structures was possible by creative instrumentation, gas chromatography and mass spectroscopy[14-18]. Isolation of several pure milligrams of PGE_1, and $PGF_{1\alpha}$ led to further structural study. Due to infrared study and micro-

hydrogenation, it was found that PGE_1 and $PGF_{1\alpha}$ both contain one trans-double bond. Also PGE_1 was identified as a cyclopentanone, whereas $PGF_{1\alpha}$ was not [19]. Borohydride reduction of PGE_1 did yield an isomeric mixture of $PGF_{1\alpha}$ and $PGF_{1\beta}$, the former identical to the substance in sheep vesiular glands. An oxidation study of PGE 1 by ozonolysis showed the absolute configurations of the lower side chain to be S due to the isolation of 2-hydroxyheptanoic acid as the corresponding acetate 2, (see scheme 1). Notice, with a 20 carbon skeleton many stereochemical variations are possible and will be accounted for in the following discussion on nomenclature.

Scheme 1 Degradation of PGE_1



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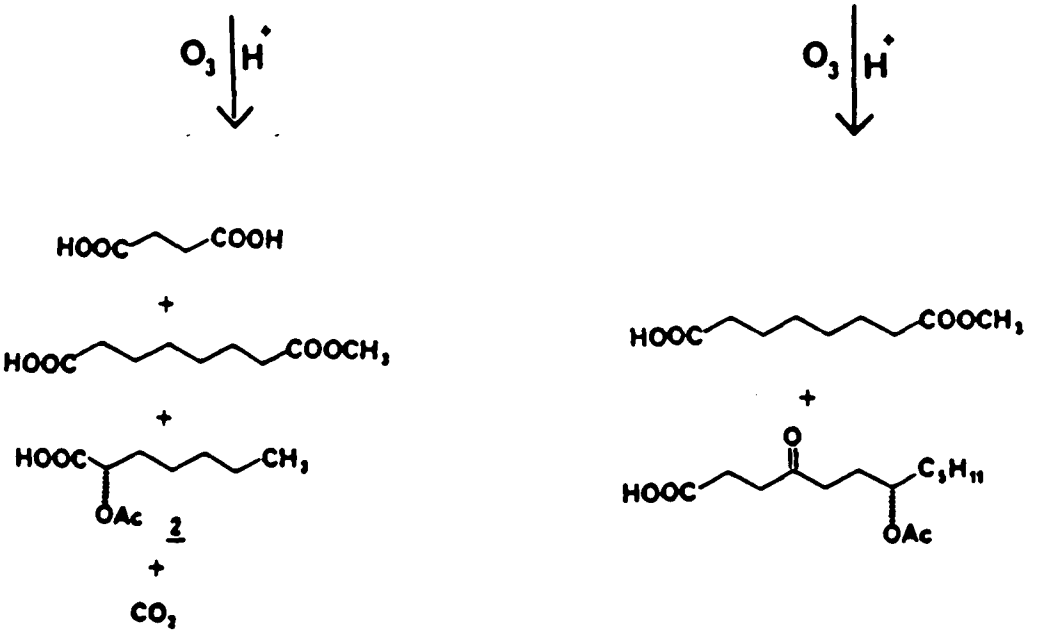
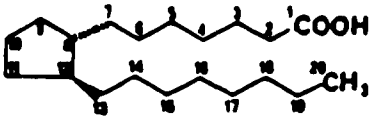


III- Nomenclature

A nomenclature system is necessary for our discussion of prostaglandins due to the many variations of the 20 carbon skeleton. IUPAC-like nomenclature would have been too cumbersome; a more simple, practical naming system would also encourage a structure- activity linkage in the medicinal use of prostanoids. The system is based on two structures: a 20 carbon carboxylic acid, prostanoic acid 3 and it's saturated hydrocarbon, prostane 4.



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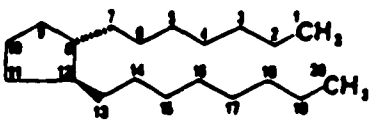

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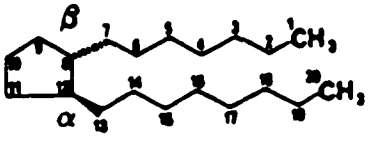
Although all known synthetic prostanoids have similar side chain configurations, stereochemical differences exist. There are four stereoisomeric possibilities: 1) the natural prostaglandin stereochemistry 5: hydrogen beta at C-8 and alpha at C-12 ; 2) ent-prostane 6, where ent (enantiomer) means alpha hydrogen at C-8, beta at C-12; 3) isoprostane 7, both C-8, C-12 side chains above the plane (beta), and cis, 4) ent-isoprostane 8, where both C-8 and C-12 side chains are below the plane and cis.



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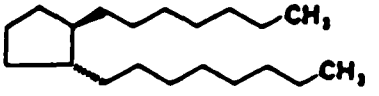

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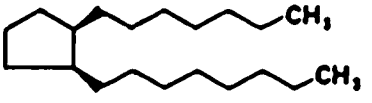

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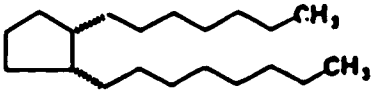

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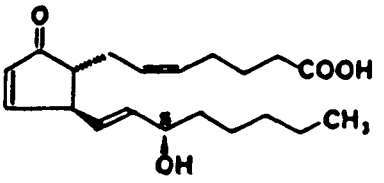
Also, double bonds found on the side chains are denoted by numerical subscripts. That is, PGA_1, has one trans double bond between C-13 and C-14 of prostanoic acid. Likewise, PGA_2 contains the trans double bond at C-13 and a cis double bond at the C-5, C-6 position. PGA_3 would contain the double bonds of PGA_2, plus a cis double bond at C-17, C-18.

There are five families of skeleton-types for prostaglandin nomenclature based on Von Euler's solubility scheme. Of course, the soluble fractions depend on substituted ring functionalities. They are: 1) PGE (ether soluble); 2) PGF (phosphate soluble); 3) PGA, formed on acid treatment of PGE ; 4) PGB, formed on basic treatment of PGE, and 5) PGD .

Additional stereochemical cyclic substituents can be named by additional subscripts: beta above the plane of the ring; alpha below. This system works if the side chains extend to the right of the ring and also it depends on the user's knowledge of natural prostaglandin configurations. Clear designations aren't supplied and substituent placement does vary with the nature of the prostaglandin. If unnatural designations exist, two sets of prefixes can be adopted. For example, compound 9, since it does not have the usual (15 s) hydroxy configuration, would be called either 15-epi-PGA_2 or 15 R-PGA_2.



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As synthetic creations have increased this nomenclature system might become inadequate to the task. In the meantime, prefixes try to compensate for changes in the basic prostaglandin skeleton. Dihydro means a double bond is gone; deoxy means one O-group is removed; oxo means a -C=O is inserted; oxa means a carbon is replaced by oxygen; aza means a carbon is replaced by a nitrogen; nor means loss of a carbon with no replacement; and homo means a carbon is inserted. Though not simple, the above system is more manageable than the standard chemical rules of nomenclature. Nelson [20] and Anderson [21] argue this idea, if you are interested.

Two anomalies or exceptions exist in this nomenclature system : PGH and PGG. Actually, PGG is a precursor for PGH and their substituents are similar but categorized differently. That is PGG, or 15-hydroperoxy, is reduced to form PGH with it's 15-hydroxy substituent, and the nomenclature system has no special compensation for this

situation. The newest synthetic prostaglandin, PGI, previously known as PGX, has an different side chain arrangement as compared to other prostaglandins[22].

IV- Occurrence & Biosynthetic Activity

Though the first prostaglandin was found in human seminal plasma, prostaglandins are present in the brain, kidneys, lungs, ovaries, intestine, stomach, pancreas and eye (in most mammals). Human seminal plasma contains 13 different types of prostaglandin, 300 micrograms total per ml of fluid. Other tissue types contain less than one microgram/ml; the amounts of prostaglandins in these tissues make detection difficult.

Potency of prostaglandins in humans is high, and daily production rarely exceeds two micrograms[23]; other animals produce even less. Natural sources of prostaglandin-like precursors for prostaglandin synthesis have proved of little help. Recently, PGE_2 and $PGF_{2\alpha}$ were isolated from red algae, but less than 0.02 % prostaglandin (in wet weight) could be extracted[24]. Mussels, frogs and other lower invertebrates produce low levels of the hormone-like chemical[25]. A rich source, containing almost 1 % by weight of a mixture of prostaglandins, is the soft coral Plexauria homomalla which exists in Caribbean waters. Compositional variation of prostaglandins depends on the area of the coral's source,

but generally include the following prostaglandins : PGA_2, PGE_2, 15-epi PGA_2 and 15-epi PGE_2.

To this date, these corals are the only industrial source of natural prostaglandin precursors[28]. Many synthetic pathways were developed in the last two decades but little industrial use of the natural precursors has emerged due to their scarcity. At present, only a few prostanoids are used medically, to induce labor, control pituatary release, stimulate smooth muscle and open bronchii. One form is also used to control oestrus in cattle.

Not all biosynthetic mechanisms are known but the E and F series are produced from essential precursor fatty acids[25], such as linoleic acid 10. Endoperoxides, PGG and PGH, are known intermediates in the synthesis of PGI and thromboxanes (TXA_2 and TXB_2)[13] from arachidonic acid 11, (see scheme 2).

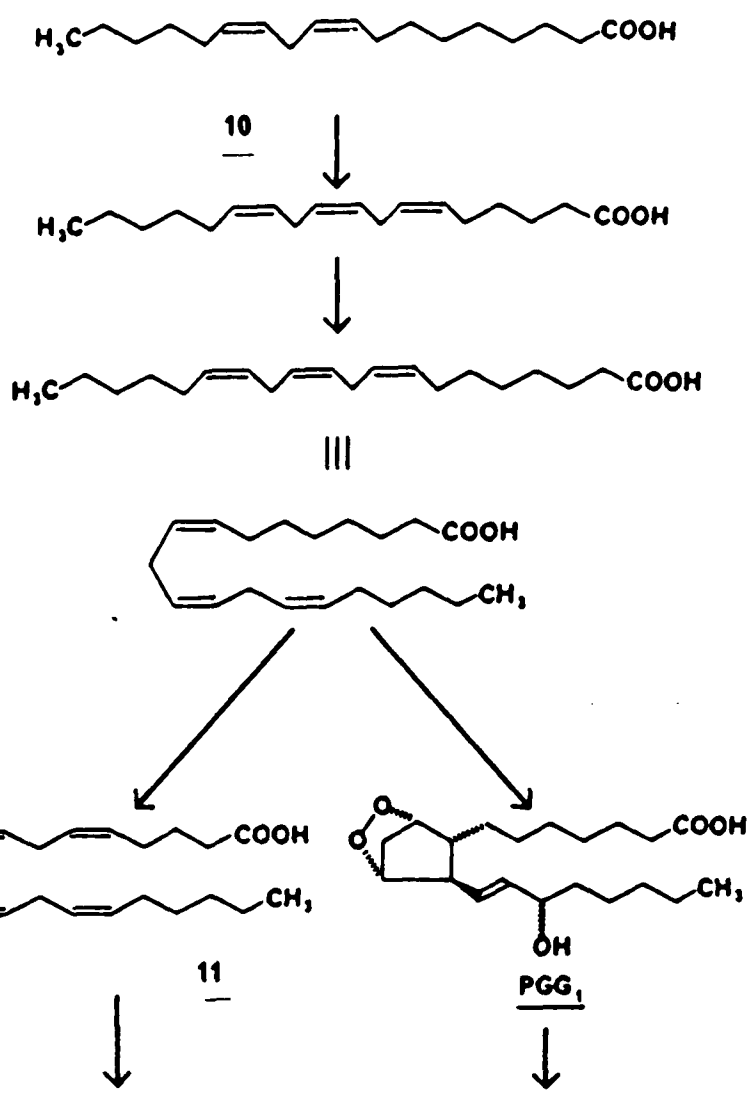
Radioactive isotopic labelling of prostanoid pathways leads us to believe that all prostaglandins originate from fatty acids, and all mammalian cell are capable of prostaglandin production[27].

Prostaglandins produce a wide range of effects in tissue, though existing in low concentration in cell mem-

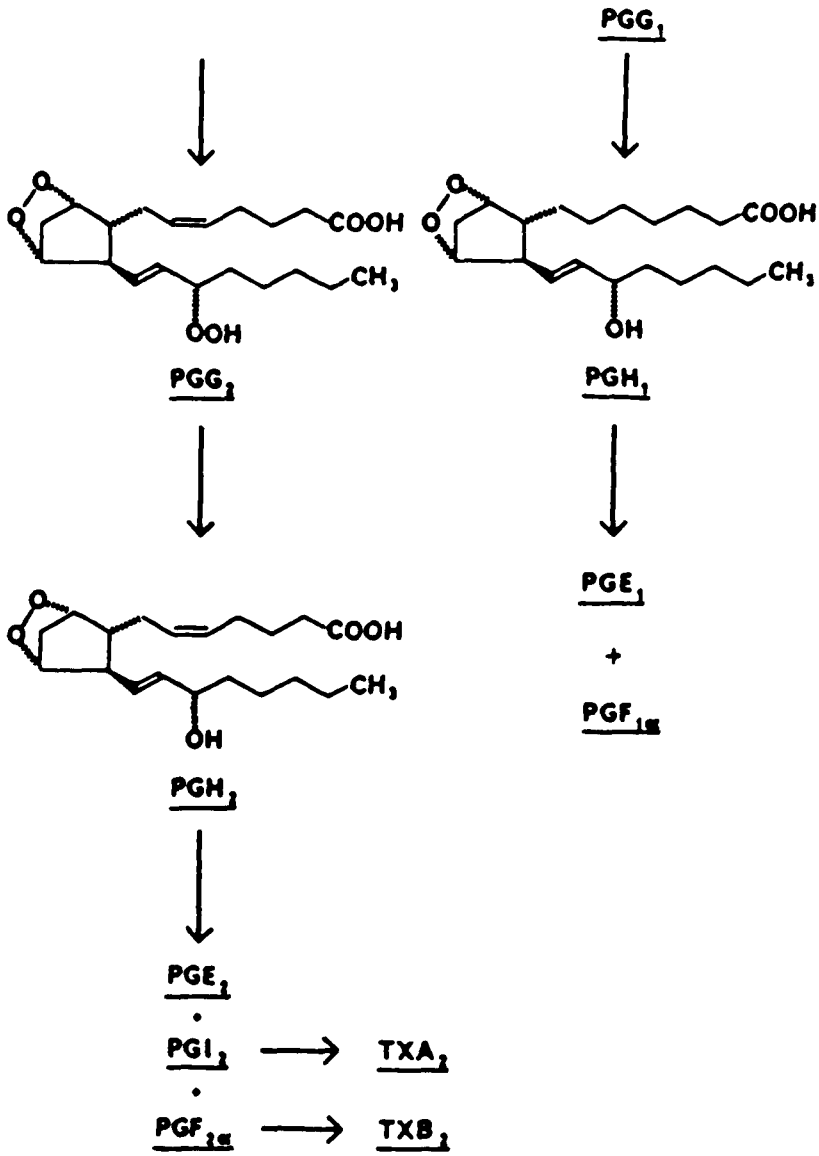
branes. There is, however, hope for finding medically useful pharmaceuticals from such small amounts of a drug. Prostaglandins principal function is considered to occur in cell membranes where they are synthesized. They play a fundamental roll in cellular metabolism and cell function[28]. In this role, prostaglandins act on tissue immuno-defense systems, which can result in fever, vomiting, pain and inflammation. Anti-inflammatory drugs act to inhibit prostaglandin synthesis as part of their effect. Such drugs include phenylbutazone, indomethacin and aspirin[29]. Prostaglandins also block the breakdown of fats and hormone release, and they constrict pupils and inhibit gastric acid production. Also, platelet aggregation is inhibited or promoted depending on the prostaglandin. Prostaglandins also act as intermediates in thyroid hormone stimulation[25].

In general, prostaglandins affect the normal functioning of the respiratory, gastric, circulatory, renal, reproductive and neurological systems . The versatility of low concentrations of prostaglandins in affecting biological activity leads naturally to attempts to produce new and specific analogs. Artificial or synthetic prostaglandins now known effect abortions, induce artificial insemination, and control asthma, ulcers, high blood pressure , arthritis and nervous system disorders.

Scheme 2


H3C
COOH
10
H3C
COOH
H3C
COOH
COOH
CH3
COOH
CH3
11
O
O
COOH
CH3
OH
PGG1

(cont'd scheme 2)



V - Synthetic Approaches To Prostaglandins

Prostaglandin synthesis is challenging because stereo-isomeric possibilities are numerous. For example, PGE_2 and $PGF_{2\alpha}$, both major series, contain 4/5 chiral centers and two double bonds in their side chains, as well as sensitive functions such as the beta- ketol function of PGE_2, which is labile to both acidic and basic conditions. Another example of functional sensitivity is the unstable enone of PGA which is subject to double bond migration. With such obstacles, it is surprising less than a decade intervened between the first isolated crystals of PGE and an unambiguous synthesis of PGE, in 1968 by E.J.Corey[30,31]. This first synthesis was long, non-stereospecific, limited to one racemic product and it's derivatives, and low in yield. Since that first synthesis the field has virtually exploded. We shall review here only the highlights and illustrate the several strategic approaches with a few examples, concentrating finally on the conversions of non-prostanoid natural precursors.

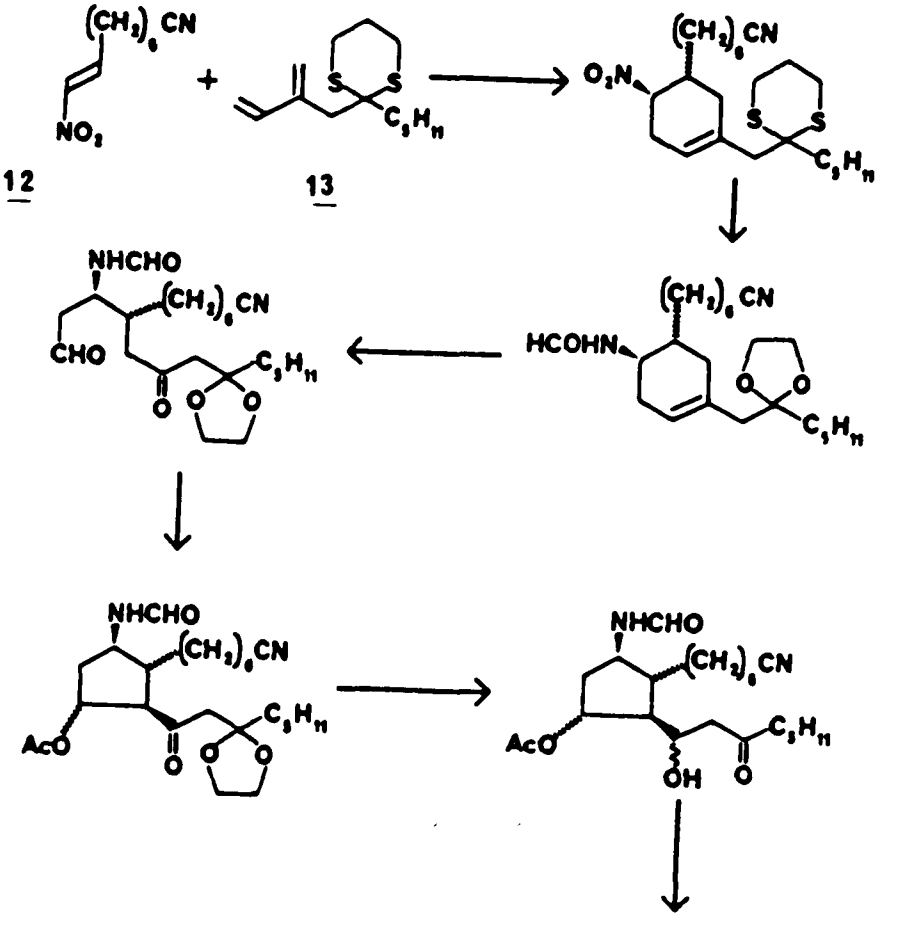
1- Acyclic Precursors

One of the earliest approaches to prostaglandins used the aldol condensation as the key step. Corey's approach was through the formation of the C-11, C12 bond, while Miyano's approach involves the formation of the C-8, C12 bond.

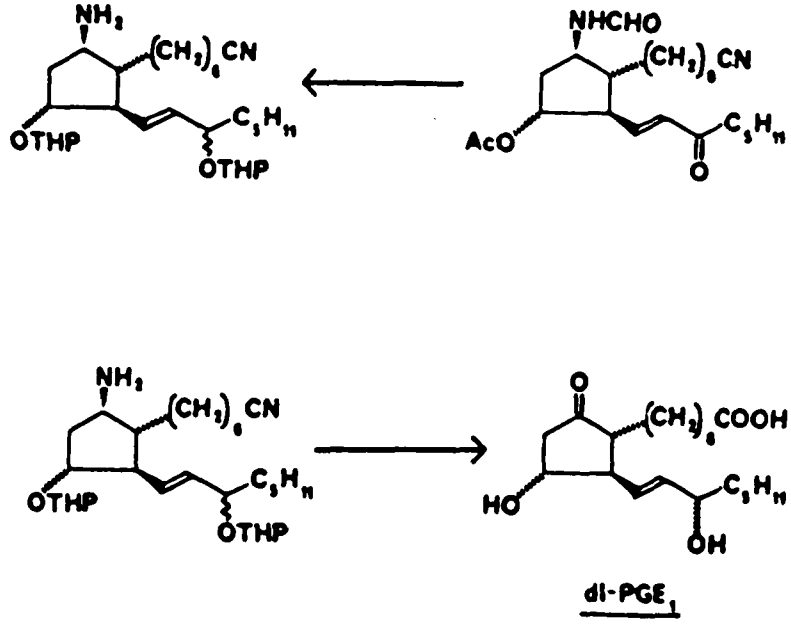
Corey[32] took advantage of two strategically placed double bonds (see scheme 3) via the Diels-Alder reaction of diene 13 and dienophile 12. The keto group of PGE_1 was also reduced to form an epimeric mixture of $PGF_{1\alpha}$ and $PGF_{1\beta}$.

scheme 3

Racemic Prostaglandin Corey Synthesis (1986)



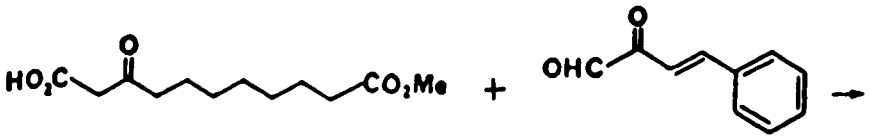
(cont'd scheme 3)



dl-PGE$_1$

Miyano's work is noteworthy because of its direct simplicity and may have considerable potential in the manufacture of analogues. Miyano[33] treated a beta-ketoacid 14 with styrylglyoxal 15 at pH around 4.7 to evolve a cyclopentane nucleus, by aldol condensation, capable of eventual conversion to PGE and PGF. Notice in this sequence the required isomer 16b was separated by chromatography and converted to the PGE and PGF series by sequential treatment with $NaBH_3CN$ and $NaBH_4$ (see scheme 4).

scheme 4



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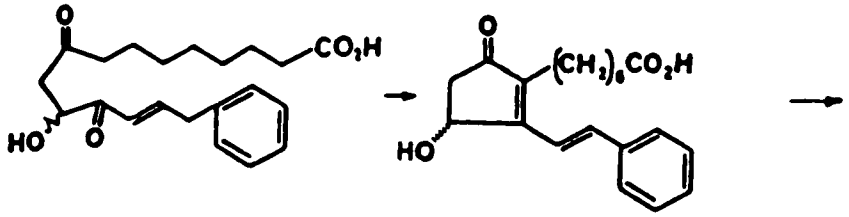
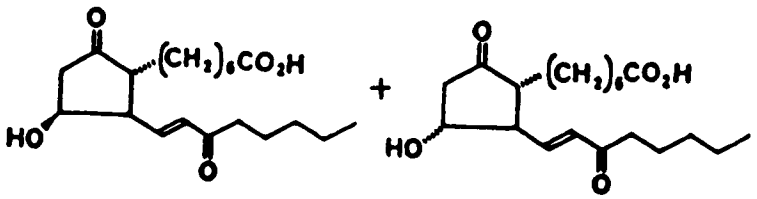
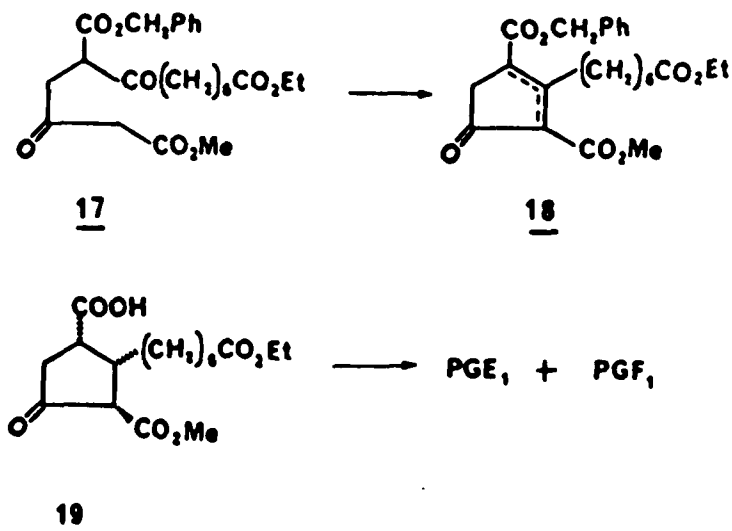




16 a 16 b

Another acyclic route, by Kojima and Sakai[34,35], involved the cyclization of diketoester 17 to give 18 and finally trans-cis cyclopentanone 19, which is capable of conversion to PGE1 and PGF1 (see scheme 5).

scheme 5



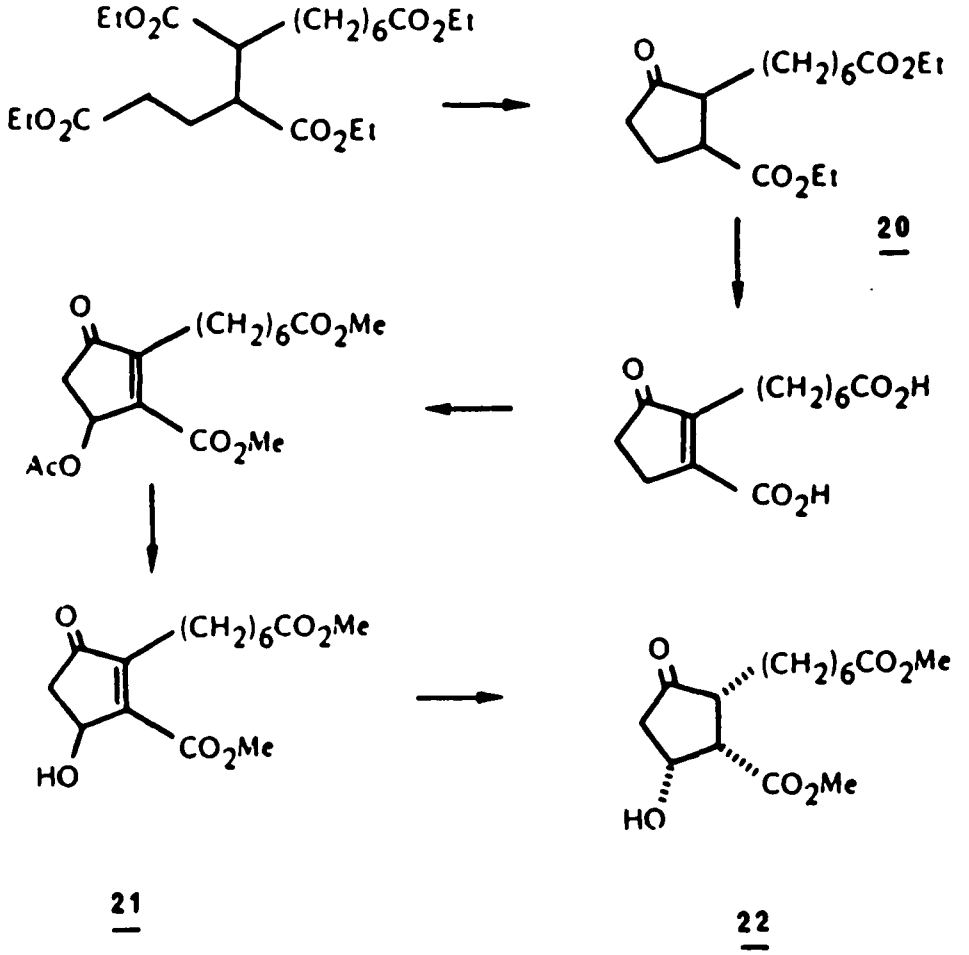
17 18

19

The last illustration of an acyclic synthesis of dl-PGE1, involving formation of the C-9, C-10 bond of a cyclopentane precursor, was reported by Finch and his associates[36]. Although the cyclopentane diester 20 was isolated in 92% yield from a readily available starting material, the approach suffers from the lack of a suitable protecting group for the C-9 carbonyl generated so early in

the synthesis. Introduction of the 11-hydroxy group has been achieved employing well-established procedures involving allylic bromination, followed by conversion into the corresponding acetate and hydrolysis. Hydrogenation of the hydroxycyclopentenone diester 21 or its silyl derivative over Raney nickel gave the all cis derivative 22.

Scheme 6



The fact that racemates generally result from acyclic precursors explains the need for syntheses involving cyclic, bicyclic, or natural precursors.

2- Bicyclic Precursors.

2.1. Bicycloheptane

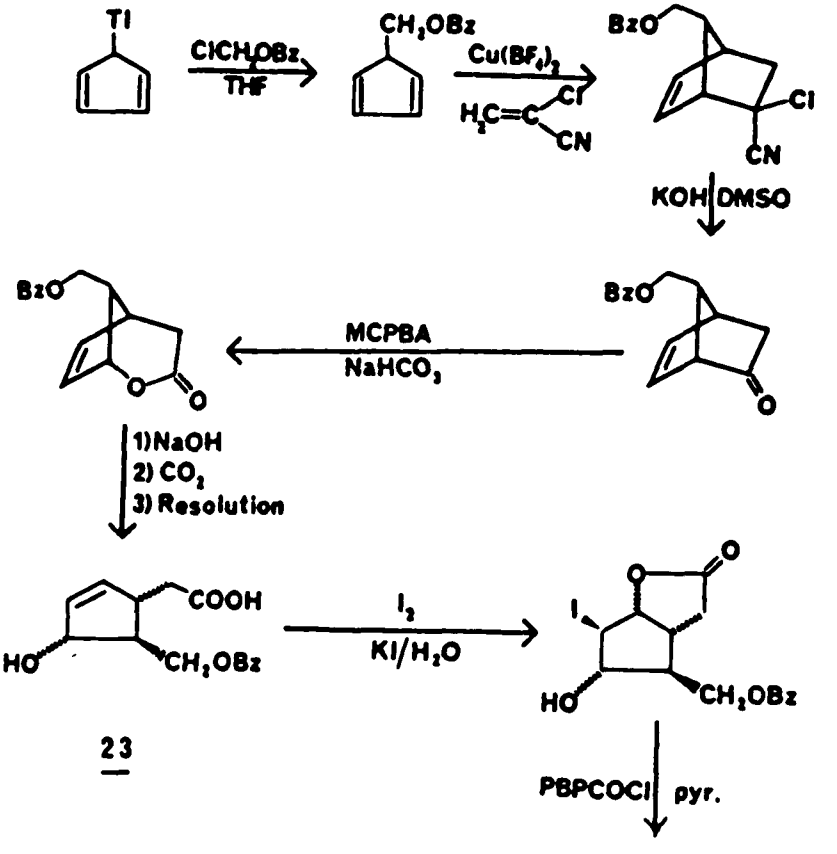
One of the most widely acclaimed and versatile approaches to the prostaglandins is the bicycloheptane approach. It was developed by Corey in 1969, as an objective to develop a practical route which would allow synthesis of the entire prostaglandin family.

Corey's bicycloheptane synthesis[37] is a very versatile sequence which allows the generation of the four asymmetric centers of the cyclopentane ring of the F series prostaglandins. In this approach carboxylic acid 23 is resolved as an (+)-amphetamine or (+)-ephedrine salt[38], resulting in the proper stereochemistry of a natural prostaglandin[30,32,41]. This ingenious synthesis, also known as the Corey lactone-aldehyde synthesis, utilizes an intermediate 24 which allows both side chains to be constructed by successive Wittig reactions. PGE_2 was produced in 23% yield and $PGF_{2\alpha}$ in 27% yield. Most syntheses mentioned from this point on will utilize a Corey lactone-aldehyde intermediate, with a varied side chain to produce alternative prostanoids.

A cyclopentadiene is alkylated with chloromethyl benzyl ether, and the geometry of the resulting bicyclic system is

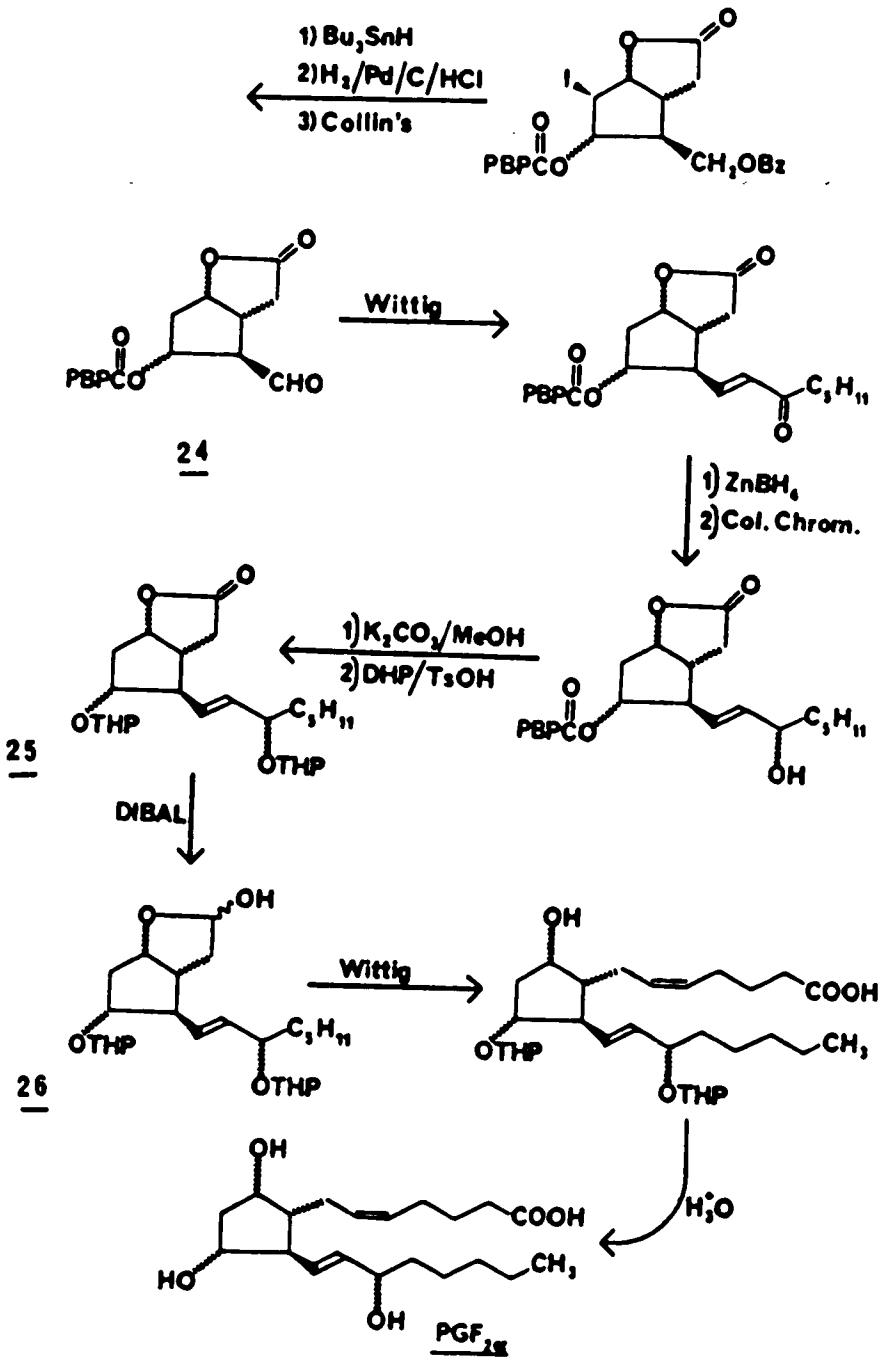
transferred to the chiral center at C-11 by Baeyer- Villiger reaction. A fourth ring chiral center is introduced through iodolactonization[30,32]. A benzyl ether at C-12 was reductively cleaved and the resulting hydroxl group was oxidized with Collins reagent to yield the aldehyde 24. On a large scale, the chlorine-methyl phenyl sulfide complex was used as the oxidizing agent[42]. Reduction of lactone 25 to lactol 26 was accomplished with DIBAL; at this point the lower side chain was added by a Wadsworth-Emmons reaction[44]. A second Wittig reaction using 5-carboxypentylidene-triphenylphosphorane[45], followed by mild acidic workup gave PGF_{2a} in 27% overall yield (scheme 7).

Scheme 7 Corey Lactone-Aldehyde Synthesis



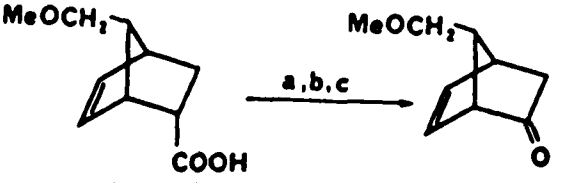
23

(cont'd scheme I)



Several other ketene equivalents have been employed with Corey's bicycloheptane approach, among them that of Trost and Tamura[46]. Their scheme utilizes acrylic acid which is an extremely effective dienophile as a starting ketene equivalent. Conversion of the Diels-Alder adduct acid 27 to the Corey bicyclic ketone 28 was accomplished by a three step decarboxylation procedure (scheme 8).

Scheme 8 Trost Rxn



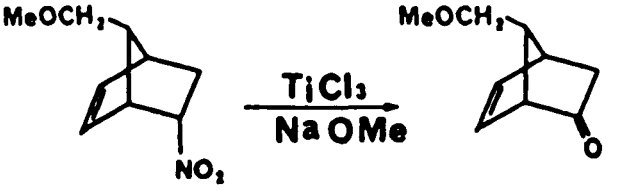
27 28

a) 2 eq. LDA followed by Me_2S_2 .

b) NCS/$NaHCO_3$/alcohol.

c) aqueous HCl .

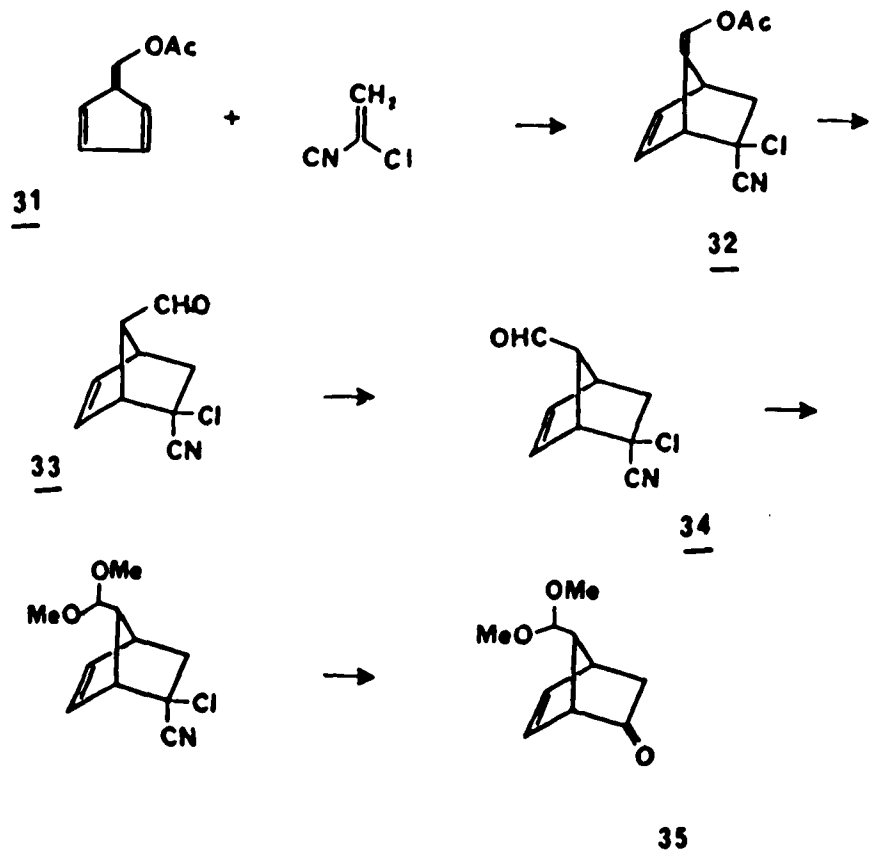
Another ketene equivalent system, utilized by Ranganathan and his colleagues[48], is nitroethylene, an excellent dienophile. The Diels Alder addition product 29 was transformed into Corey bicyclic ketone 30 by a procedure of McMurry's[49], (using sodium methoxide and titanium trichloride).



29 30

Another useful method of forming Corey aldehyde was accomplished by Brown[53] and colleagues, using 6-acetoxyfulvene 31 as starting material. Formation of Diels Alder adduct 32 , followed by acid hydrolysis yielded 33 which isomerized to a more stable product 34. Conversion to ketone 35 followed protection of the aldehyde 34. Once the aldehyde was obtained the remainder of the synthesis utilized the Corey scheme (see scheme 9).

Scheme 9 Acetoxyfulvene Approach

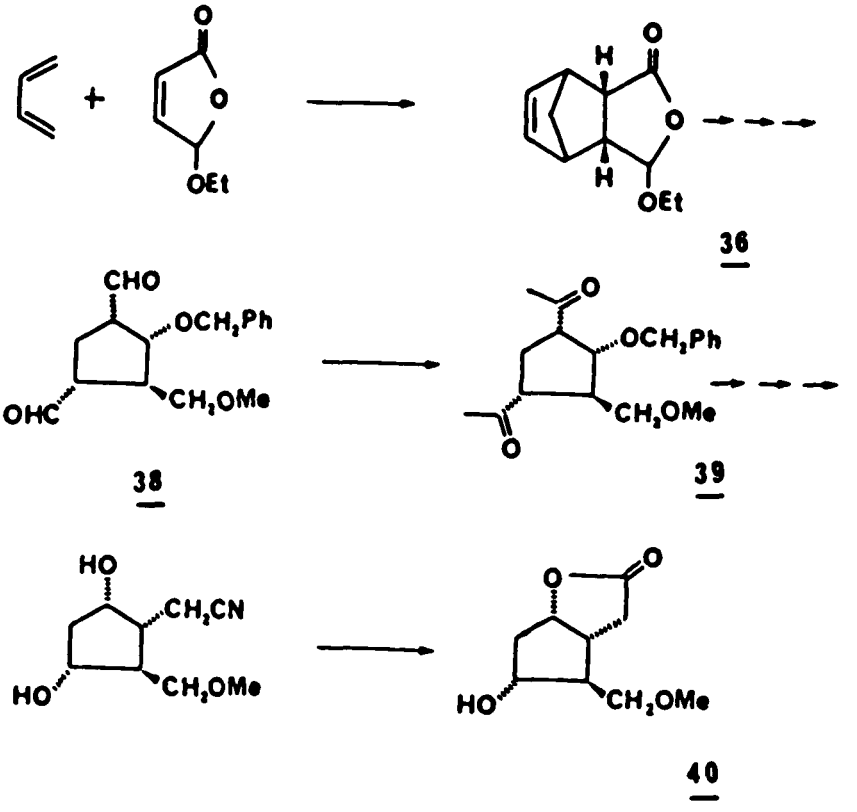


Another bicycloheptane approach, employing oxidative cleavage of double bonds was conceived by Jones and his colleagues[54,55] who commenced with a norbornene derivative 37 bearing two differentially protected one-carbon pendants destined to become the C-8 and C-12 substituents. The lactone and acetal of 36 are reduced, after protection, in

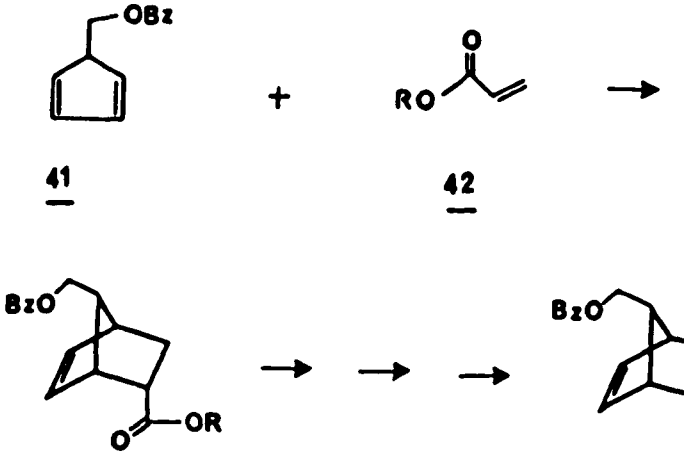
stepwise fashion. Then, oxidative cleavage of the double bond to give dialdehyde 38, conversion to diketone 39 and Baeyer-Villiger oxidation add the necessary hydroxyl groups at C-9 and C-11. Displacement with CN^- and saponification yield a Corey lactone 40 on acid workup (see scheme 10).

Scheme 10

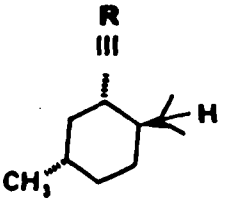
Jones Oxidative Bicycloheptane Approach

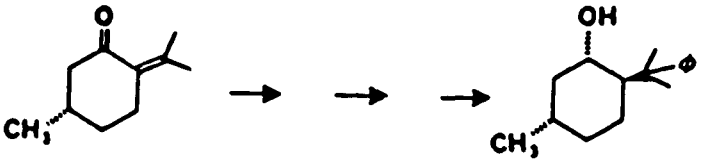


The elegant approach achieved by Corey and his group is undoubtedly to be regarded as a milestone, representing the first total synthesis of an optically active natural prostaglandin. Corey has also formed an optically active bicyclic ketone 43 utilizing a Lewis acid catalyzed Diels-Alder reaction of cyclopentadiene 41 with (-)-menthyl-acrylate 42 to give an adduct with up to 5% asymmetric induction. Corey and Ensley[47] have found that the chiral alcohol 45 prepared from s-(-) pulegone 44 is superior to that from (-)-menthol as a chirality transfer agent. However, this is considerably more costly since the pulegone is first synthesized from (-)-citronelol.



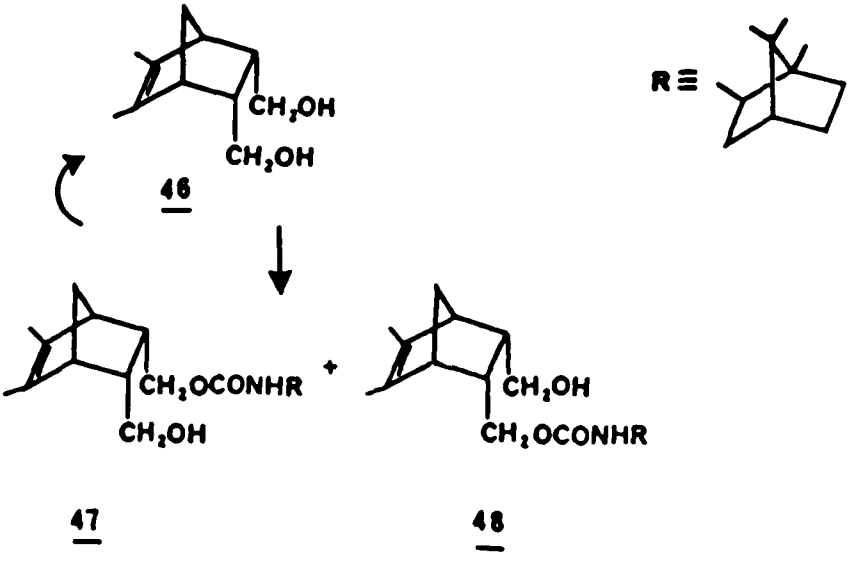
41 42 43





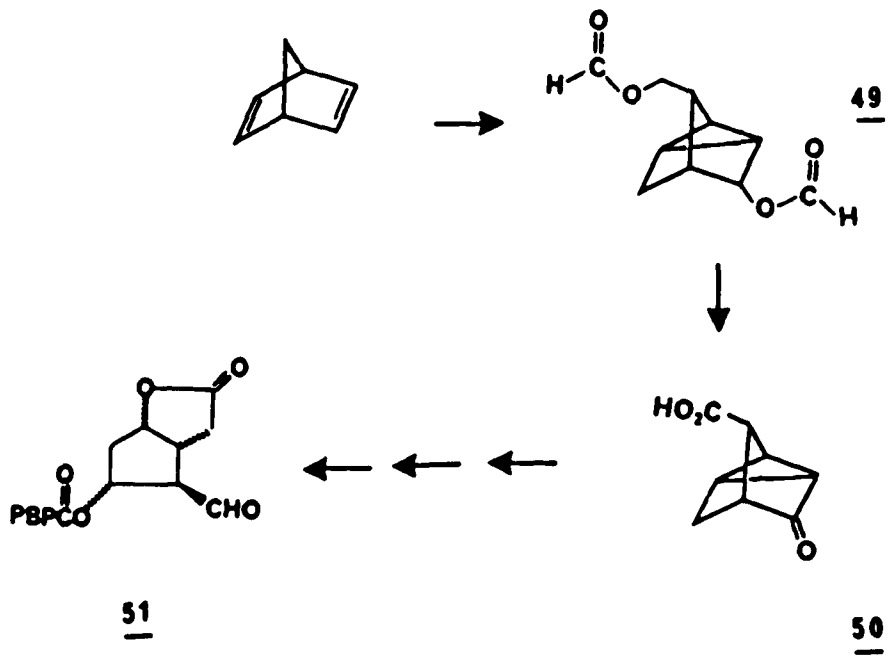
44 45

The Hoffman La-Roche group[80], started with a symmetrically substituted norbornene: meso-alcohol 46, upon treatment with phosgene and then with isobornylamine (chiral reagent), gave a mixture of diastereomers 47 and 48 separable by fractional crystallization. Since the undesired enantiomer 47 was hydrolyzed back to 46 and recycled, the chiral efficiency of this synthesis is very high (as shown below).



A similar reaction was developed simultaneously by a Pfizer group[50] and Sutherland/Peel[51]. Both groups independently used a Prins reaction[52] on norbornadiene as the key step to give 49. Jones' oxidation of 49 led directly to tricyclic ketoacid 50 which was then converted to the Corey lactone aldehyde 51 (see scheme 11).

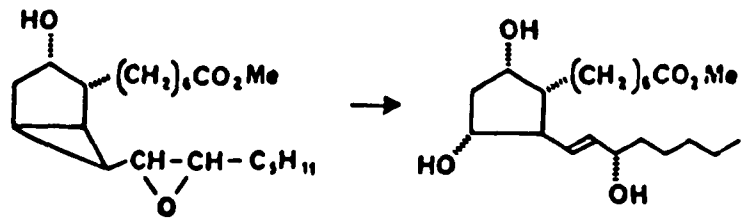
Scheme 11 Pfizer /Sutherland /Peel scheme



2.2. Bicyclohexane

An approach to prostaglandin based on cleavage of bicyclohexane precursors was first utilized by Just and Simonovitch. The key step was based on the idea that solvolysis of simple bicyclic tosylates results mainly in opened-ring products.

In the Just and Simonovitch synthesis[72], modified by the Upjohn group[73], a bicyclic epoxide 52 was treated with formic acid at room temperature or CF_3COOH at 40°C to isolate 2-3% of dl-$PGF_{1\alpha}$. That is:



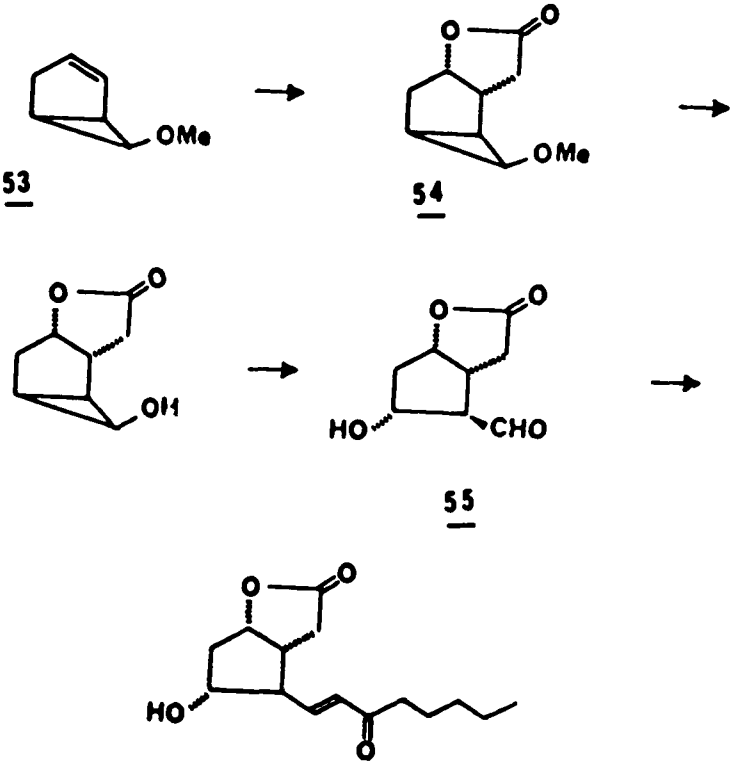
52

dl-$PGF_{1\alpha}$ methyl ester

The Upjohn modification included an osmium tetroxide oxidation which resulted in a mixture of four diastereomeric glycols. Upon treatment with acetone/water a 5% yield of dl-PGE_1 was isolated. This procedure was also used by Just and Ferdinandi[74] to prepare dl-PGE_2 methyl ester. Finally, the Upjohn group found that when an endo-bicyclohexane isomer derivative was treated under similar condition, the yield of PGE_2 methyl ester was improved to 15%.

Corey[75] utilized bicyclohexene 53, which, heated with dichloroketene followed by dechlorination and Baeyer-Villiger oxidation, gave 54. Cleavage with BBr_3 and oxidation gave Corey aldehyde 55 (See scheme 12).

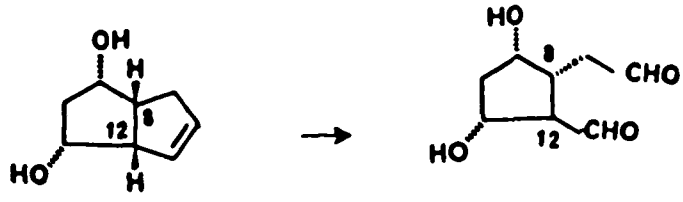
Scheme 12 Corey Bicyclohexene Approach



2.3. Bicyclooctane

This approach to prostaglandin based on cleavage of one of the rings in a suitably functionalized bicyclooctane precursor may be used to generate the prostanoid cyclopentane nucleus bearing suitable substituents for attaching the two side chains.

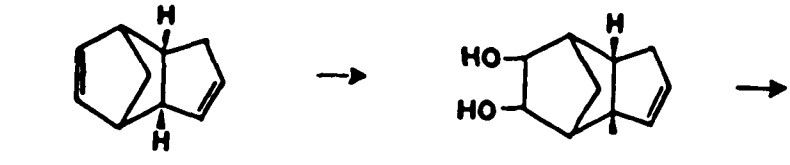
Turner et al.[78] used this approach to prepare the key aldehydic synthon 57 from bicyclooctane 56 and converted it to PGF_{2a}.



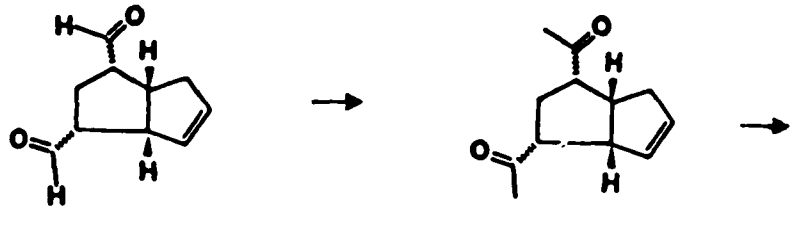
56 57

In Turner's synthesis the starting material was inexpensive endo-dicyclopentadiene 58 which formed a glycol 59 in cold $KMnO_4$. The crystalline endo-dialdehyde 60 was produced selectively since the norbornene double bond of dicyclopentadiene is the more reactive of the two double bonds present in the molecule. Once 61 , a Corey lactol, was formed, conventional chemistry was used (See scheme 13).

Scheme 13 Turner's Synthesis

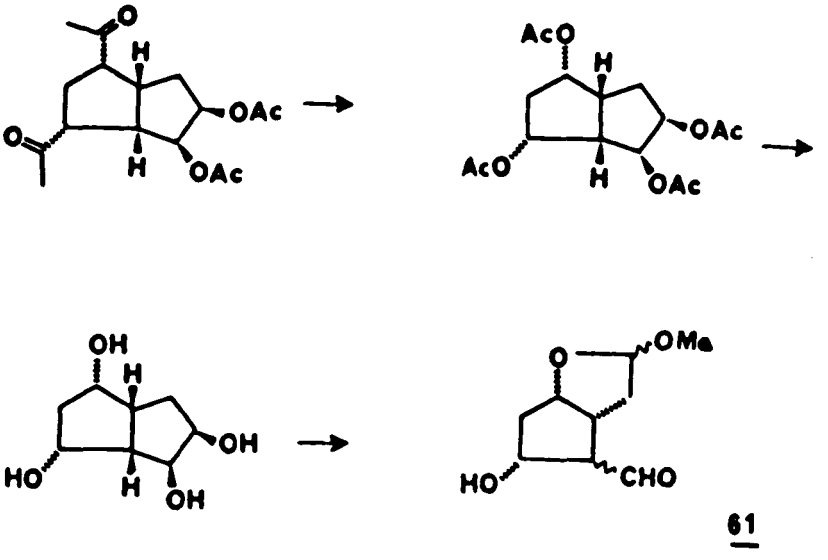


58 59



60

(cont'd scheme 13)



61

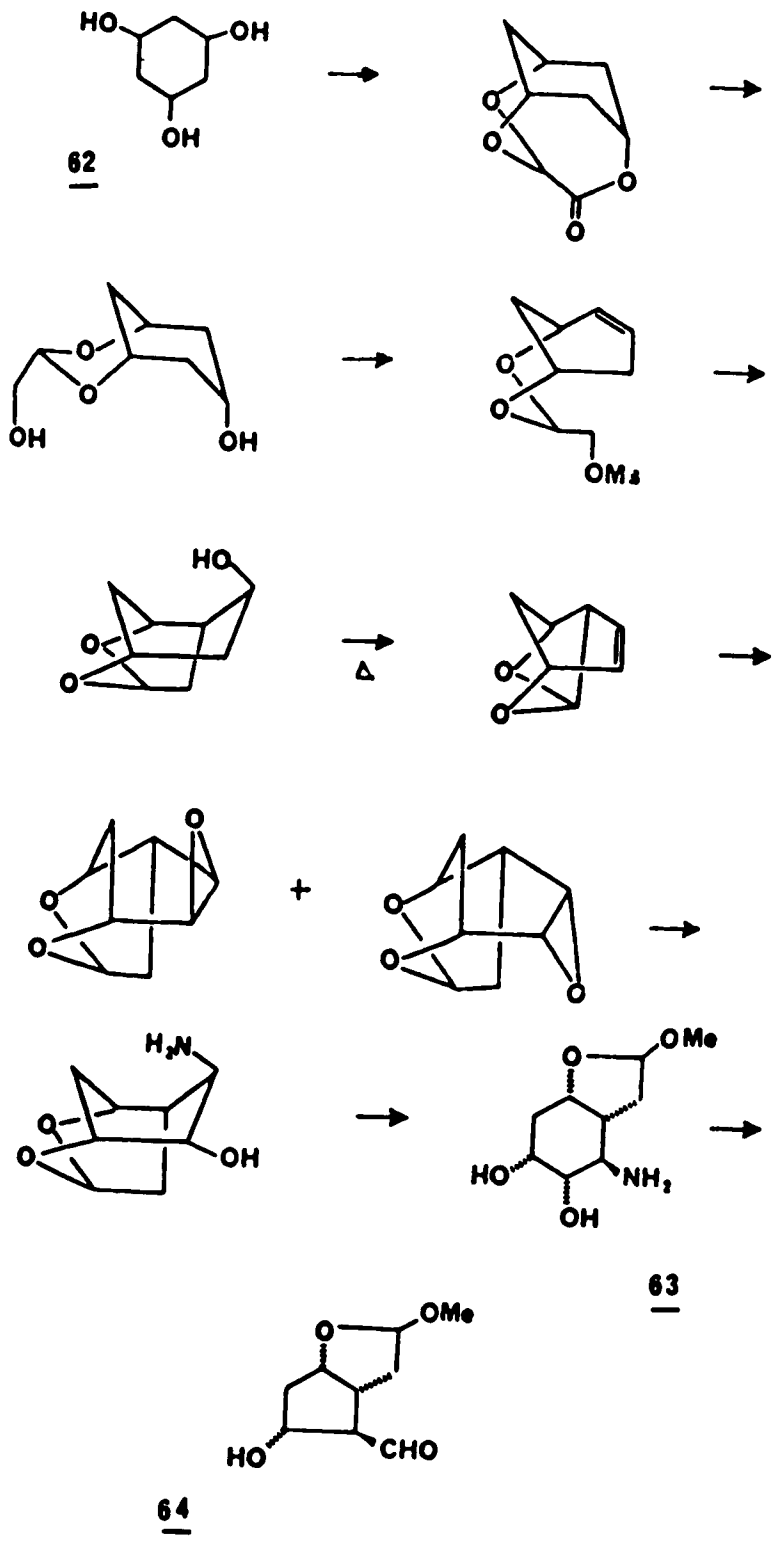
3- Cyclic Precursors

3.1. Cyclohexane:

An important approach to prostaglandins involves contraction of six-membered carboxylic precursors for production of the appropriately functionalized cyclopentane nucleus. The strategy has proved quite effective, owing to the large variety of efficient ring contraction procedures.

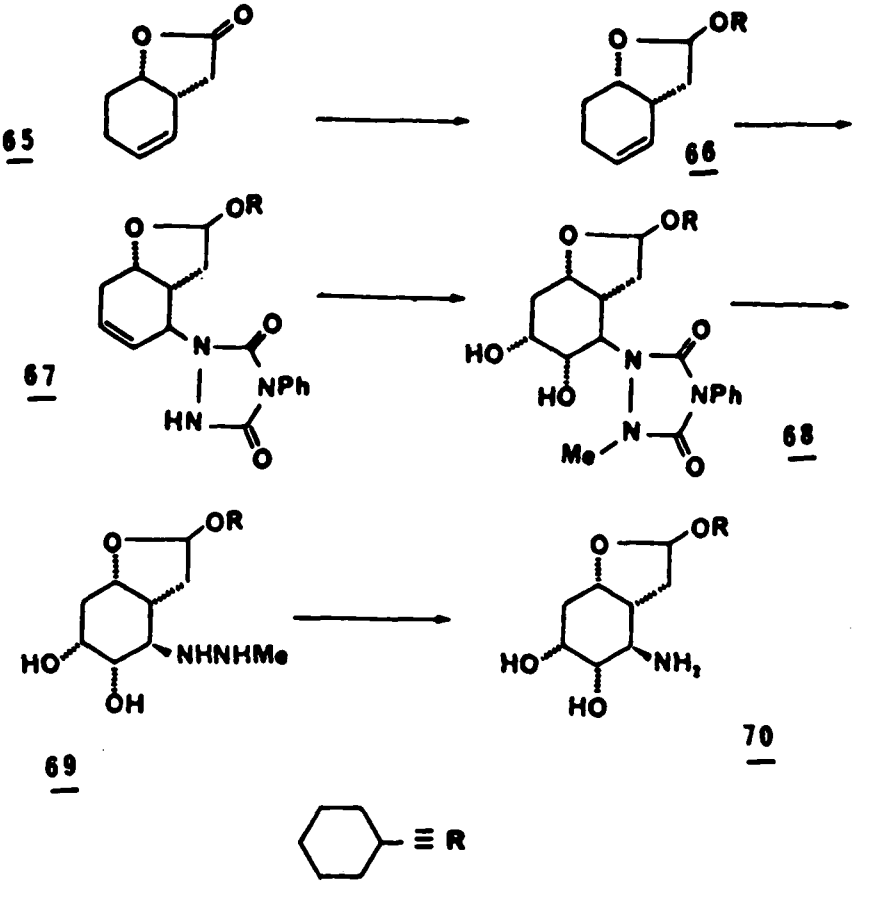
Specifically, Woodward and colleagues[56] developed an ingenious stereospecific synthesis of $PGF_{2\alpha}$ from cis-cyclohexane 1,3,5 triol 62. Stereospecificity of this reaction is due to pinacolic deamination and ring contraction of derivative 63 , (see scheme 14). This ring contraction of the key intermediate was accomplished through diazotization and mildly basic conditions, resulting in hydroxyaldehydeacetal 64.

Scheme 14 Woodward Synthesis

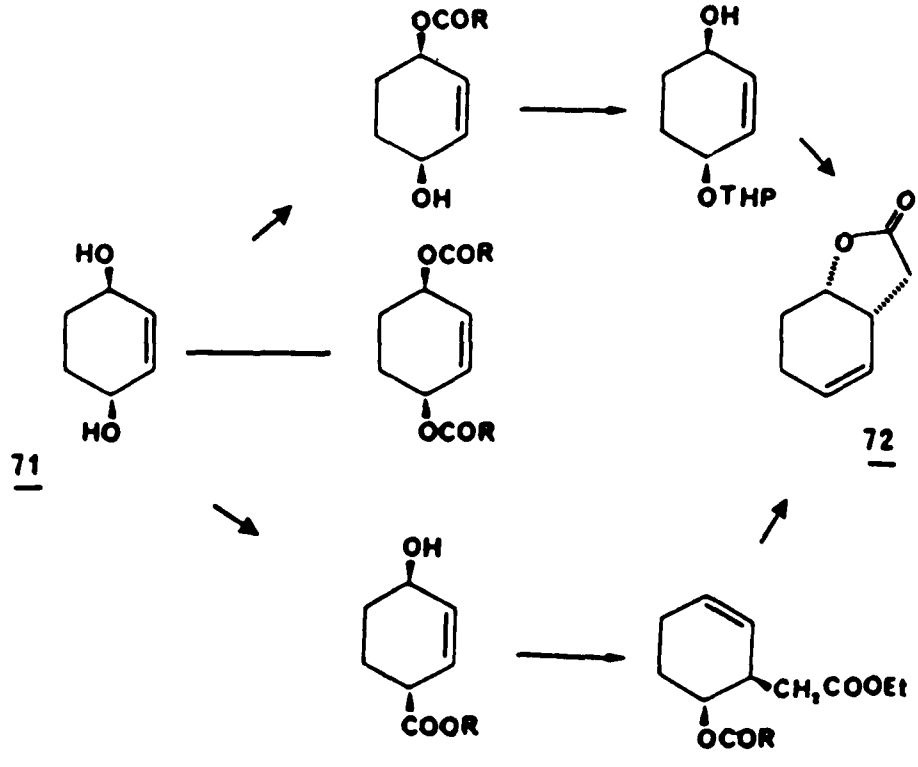


Corey and Snider[57] established another cyclohexene route from readily available lactone 65. Protection of the hydroxyl function after reduction of the lactone, gave compound 66. N-phenyltriazolinedione and 66 underwent an "ene" reaction, and the allylamine derivative was isolated in 44% yield. Methylation of 67 followed by hydroxylation of the double bond with osmium tetroxide gave 68. Hydrolysis of the triazole molecule 68 afforded hydrazine 69 which was washed over Adam's catalyst to give amine 70. The ring contraction was achieved using a procedure similar to that of Woodward et al.[58] (see scheme 15).

Scheme 15 Corey & Snider Synthesis



Terashima and his associates[89] have converted cis-cyclohexene-1,4-diol 71 to the optically active cyclohexene-lactone 72, as shown below. This cyclohexenelactone is an important prostaglandin intermediate as previously shown by Corey and his co-workers[84].



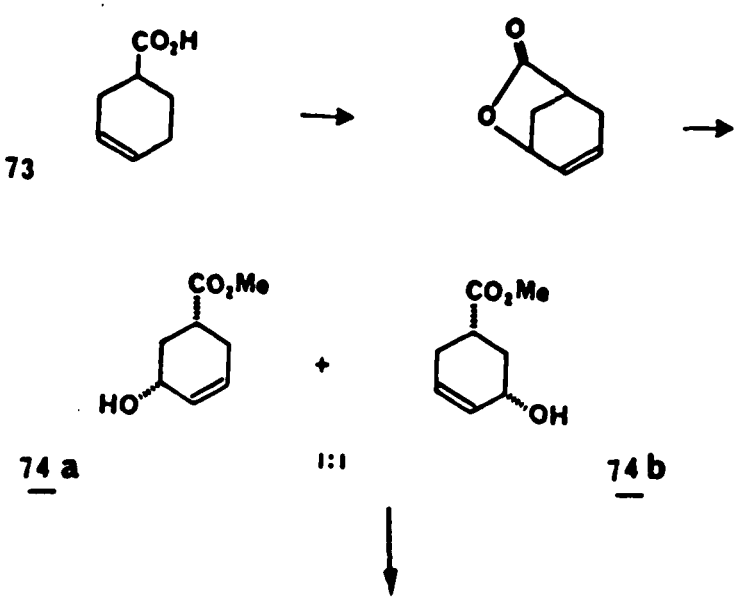
In the last approach, by Trost[88], which resulted in an optically active product, there is no intrinsic loss of material, unlike the more common approaches which rely on classical chemical resolution and loss of the undesired enantiomer. After separation of the required enantiomer, equilibration of the remaining mixture allowed further isolation of the desired material, and thus eventually, high

conversion of a racemic mixture to either enantiomer.

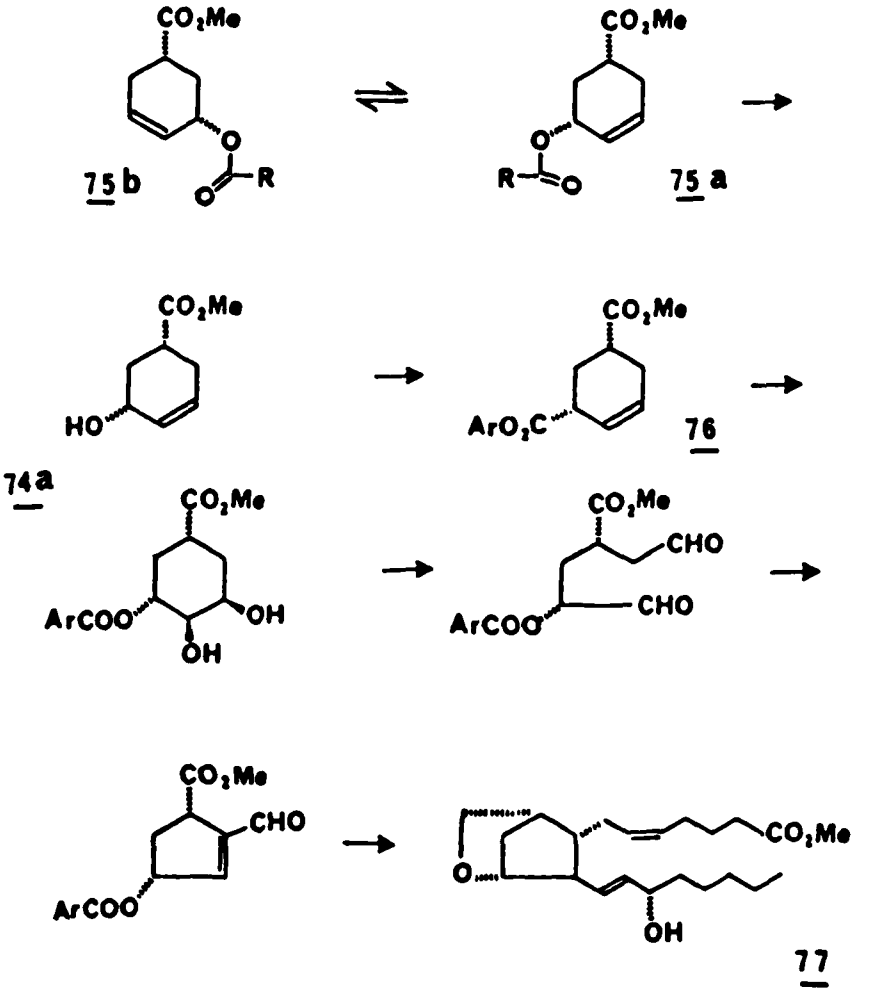
The Diels-Alder adduct 73 gave a 1:1 mixture of the allylic alcohols 74 a & b, as shown in scheme 25. The urethanes (75a and 75b) of 74 and an optically active amine were brought into equilibrium by a mercury (II) trifluoroacetate catalyzed allylic rearrangement. The required diastereoisomer 75a was separated and the remainder was subjected to the equilibrium conditions again. Thus the racemate was converted eventually to the single enantiomer 74a.

The p-phenylbenzoate ester 76 of 74a was hydroxylated with osmium tetroxide and cleavage of the glycol followed by condensation of the dialdehyde provided a chiral prostaglandin intermediate. Several prostanoids can be prepared from this intermediate, however Trost carried this intermediate to known prostanoid 77 (see scheme 16).

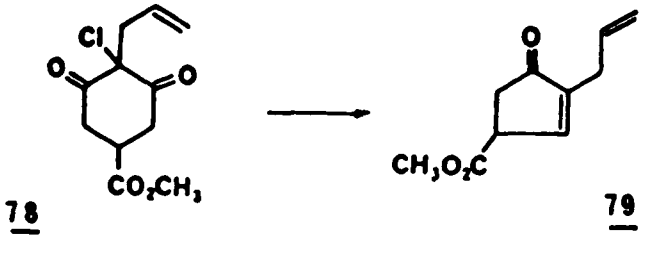
Scheme 16 Trost's Approach



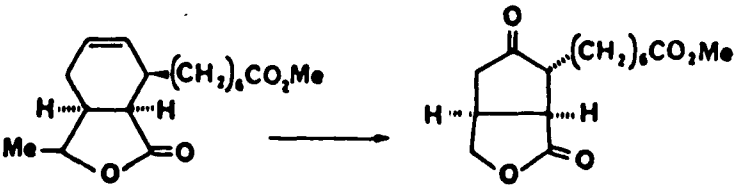
(cont'd scheme 16)



Rosen and his co-workers at Hoffman-la Roche[58] tried a Favorskii ring contraction of 2-chloro-alkylcyclohexane 1,3-diones 78 to gain a cyclopentane nucleus 79 .



Another way to get a cyclopentane nucleus 81 is from cleavage of cyclohexene intermediate 80. The resulting diacid was cyclized to the desired compound, by Kuo and co-workers at Merck[59].



80 81

3.2. Cyclopentane:

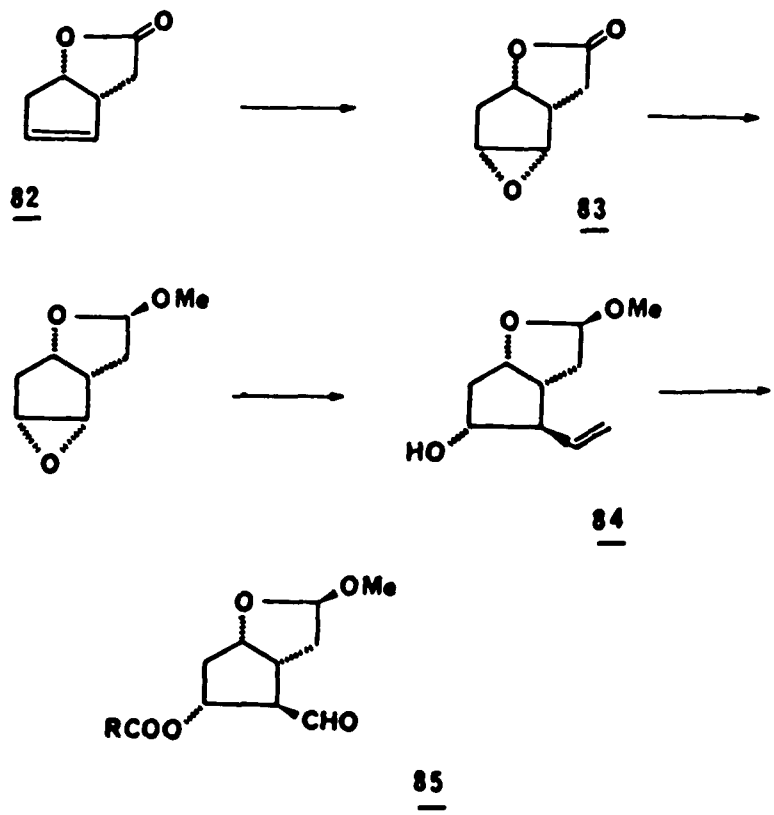
A number of approaches to prostaglandins commence with a preformed cyclopentane nucleus bearing the requisite functionality for elaboration of at least one of the side chains. The second chain may be attached by a variety of methods. The most successful varients of this general approach are epoxide opening and the conjugate addition of an organo metallic derivative.

First, nucleophilic opening of cyclopentane epoxide was studied by Corey, Fried and Stork.

The Corey synthesis[60] started from lactone 82. The desired epoxide 83 was isolated in 89% yield upon treatment of 82 with 40% peracetic acid in acetic acid. Regiospecific opening[61] of the epoxide after reduction and protection gave an over 90% yield of alcohol 84. Protection of the hydroxyl

function as a urethane and cleavage of the double bond (osmium tetroxide/periodate) yielded a well known prostaglandin aldehyde intermediate 85 (See Scheme 17).

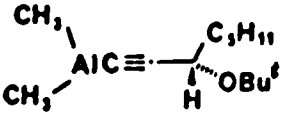
Scheme 17 Corey Synthesis



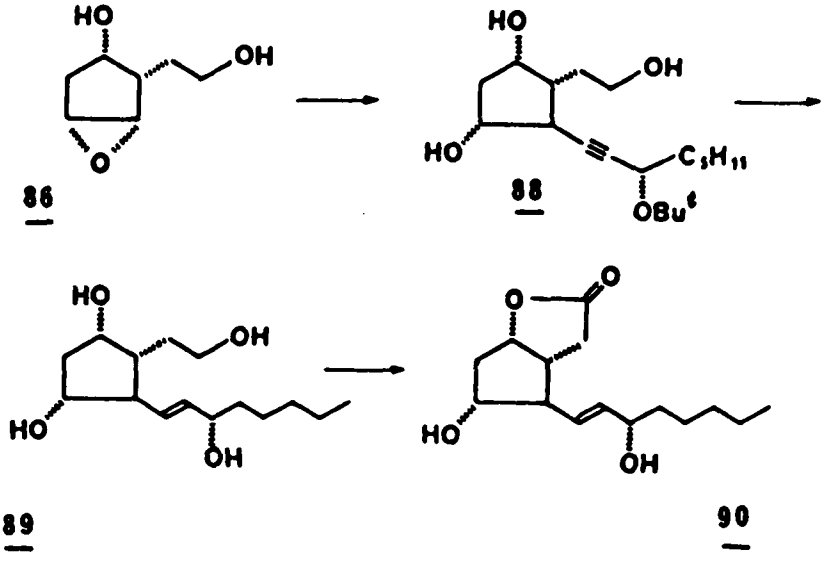
Fried and his collegues[62,63] worked out a lactone synthesis from a stereospecifically opened epoxide. Fried treated epoxide 86 with alane 87 to obtain 88 in 62% yield. Loss of the silyl group, then transformation of the triple bond to a double bond, gave 89. The desired 15(S) isomer was obtained by chromatography after selective tritylation

of the primary alcohol. Secondary hydroxyl group protection, then detritylation followed by oxidation (Pt/O_2) and base hydrolysis afford the Corey lactone 90 . It was noticed later that 89 could be converted to the Corey-lactone directly with (Pt/O_2) in 50% yield (See scheme 18).

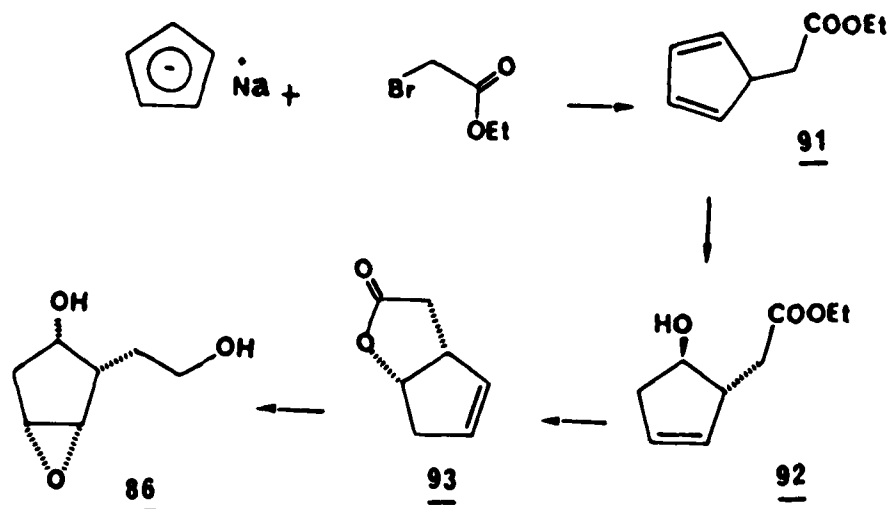
Scheme 18 Fried Synthesis



87



The epoxide 86 (Fried's intermediate) has been made in optically active form by Partridge[89] by a simple route using (+)-3-pinanylborane as the asymmetry inducing agent as shown:

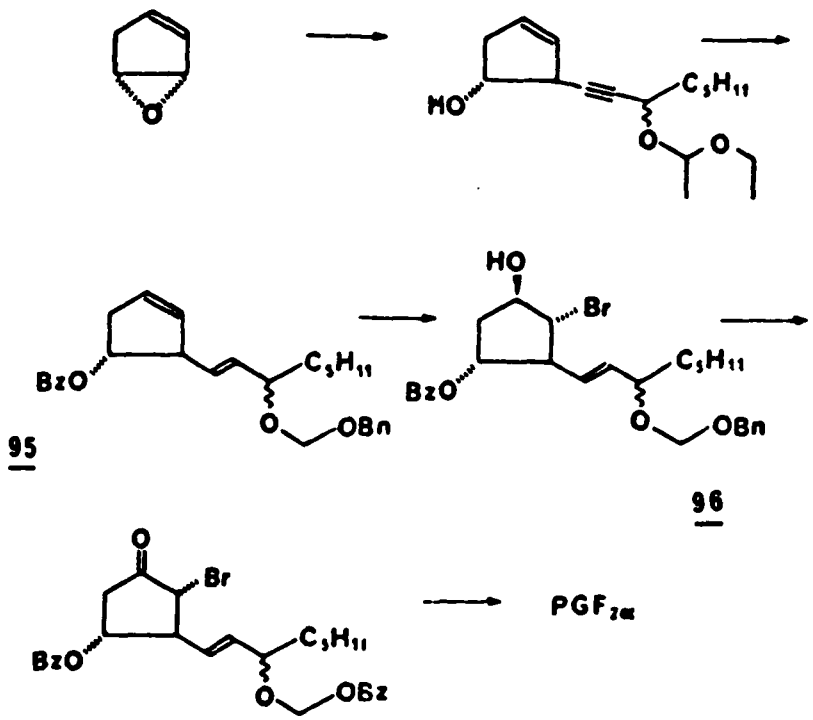


The key to this approach is an asymmetric hydroboration which proceeds in reasonable yields to furnish the product in high optical purity, without having to resort to a chemical resolution. Treatment of cyclopentadiene ester 91 with the chiral agent gave a 45% yield (96% optically pure) of 92 which, after mesylation, hydrolysis and lactonization gave 93 in 40% overall yield from cyclopentadiene. Reduction of 93 using LAH followed by epoxidation gave Fried's intermediate in greater than 90% yield.

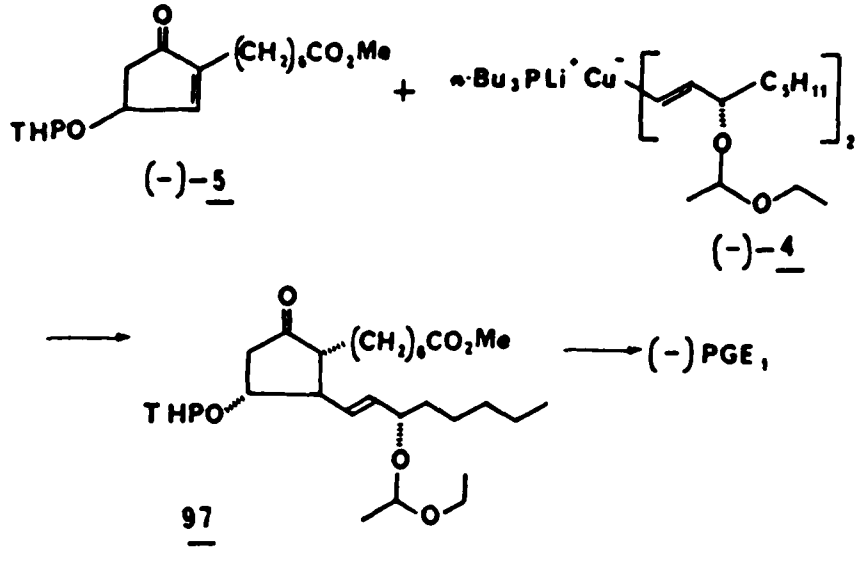
In the Stork synthesis[64] cyclopentadiene oxide 94 was treated with the lithium salt of the ethoxyethylether of 1-oct-yne-3-ol giving a cyclopentenol in 45% yield. The free

hydroxy group was protected as a benzyl ether, and following selective removal of the ethoxyethyl group, the triple bond was reduced with LAH. The resulting allylic alcohol was protected with benzyl chloromethyl ether to give 95. This was converted to bromohydrin 96 by regiospecific addition of hypobromous acid (NBS in DMSO-H_2O). Oxidation of 96 with Jones'reagent followed by addition of the top chain completed the synthesis (see scheme 19).

Scheme 19 Stork Synthesis

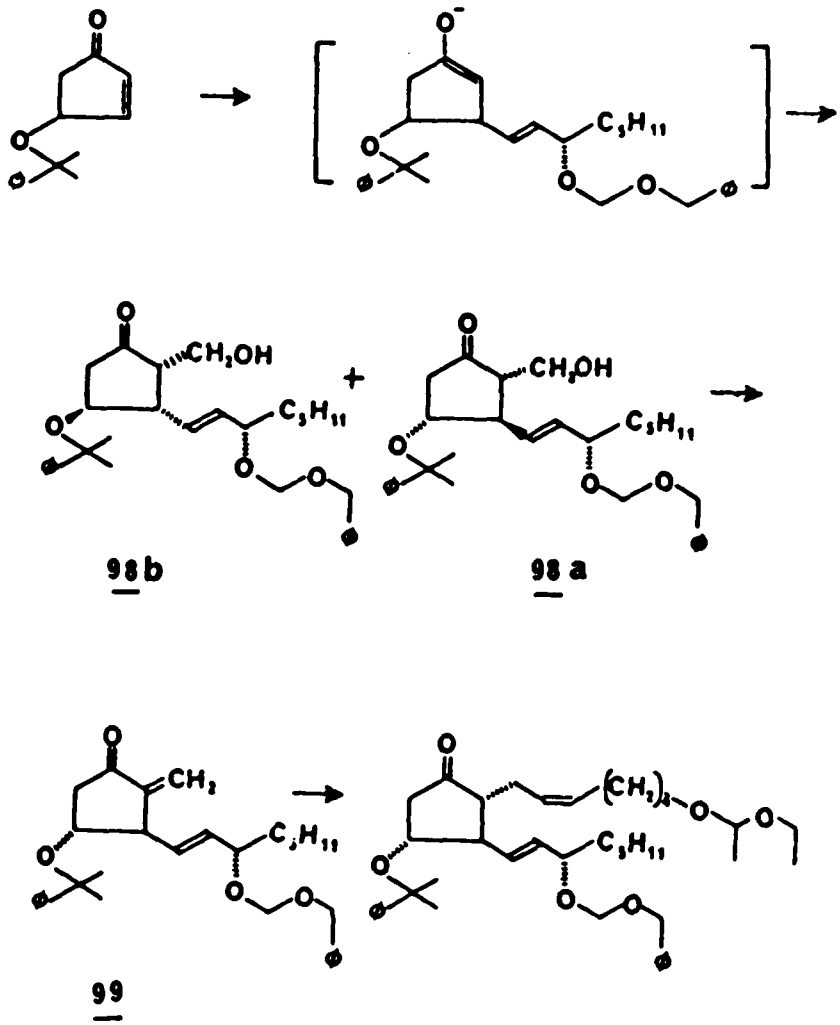


The other method of cyclopentane utilization, is the conjugate addition of organometallics to suitably substituted cyclopentenones, as done by Sih[65], Stork and Isobe[66]. Sih and his collegues conducted the first conjugate addition to a substituted cyclopentenone to synthesize 15-deoxy PGE_1. Sih also extended this synthesis to the formation of PGE_1[67,68]. Treatment of the cuprate (-)-4 with (±)-5 produced two diastereomers 97 which, after removal of the protecting groups and cleavage of the ester group with Baker's yeast followed by chromatography, furnished (-) PGE_1 and (+)-15-epi-ent-PGE_1. When the optically active cyclopentenone (-)-5 was used for the coupling, only (-)-PGE_1 methyl ester (65-70% yield based on 5) was obtained[69,70].



Stork and Isobe[68], utilized conjugate addition followed by capture of the enolate anion with formaldehyde. Hydroxymethylcyclopentanone 98a was mesylated and beta-elimination gave methylenecyclopentanone 99. Conjugate addition was again used to introduce the second side chain[71] (See Scheme 20).

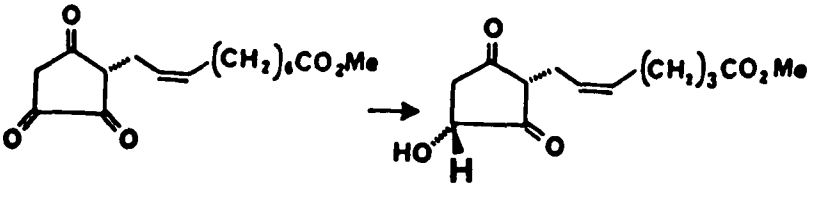
Scheme 20 Stork & Isobe Conjugate Addition



4- Consideration of Optical Activity

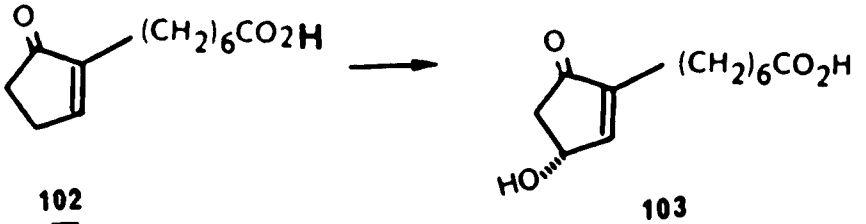
Since prostaglandins are chiral and not easily resolvable. Starting materials must be resolved in the laboratory, or by nature. In the previously discussed syntheses we have discussed introduction of optical activity by resolution of racemic mixtures or meso compounds. An example of a naturally optically active precursor prostanoid was found by Weinheimer and Spraggins[77] in the soft coral plexaura which has high amounts of prostaglandin A. Yields for conversion of PGA to E and F active forms were, however, extremely low, making this known optically active source expensive if developed.

Another way to induce optical activity in prostaglandins is through microbial transformation. Sih et al.[69] performed a microbial reduction of 100 using washed cells of Dipodascus Uninucleatus microbe to obtain 11-(R)-alcohol 101 in 48% yield (100% optical purity) as shown below.



100 101

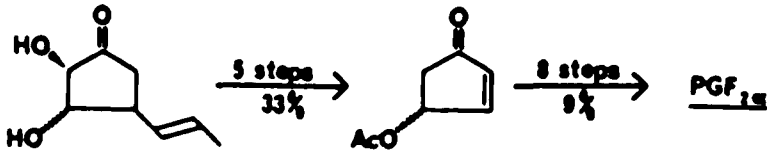
A Japanese group[30] has reported the microbial hydroxylation of enone acid 102 by Aspergillus Niger to 103 with partial asymmetric induction (optical purity of about 60%).



102 103

5- Naturally Resolved Precursors

A metabolite of the fungus Aspergillus fischerii,[83,84] terrein, 104, has been used as an intermediate in prostaglandin synthesis (see below) but the overall yield was less than 3% .



104 Terrein

Syntheses with natural, resolved, starting materials to avoid resolving schemes have been done using terrein, L-rhamnose[78], D-glyceraldehyd[79], D-glucose[80], (+)D-tartaric acid[81], and S-malic acid[82]. Most of these are attractive for prostaglandin synthesis, but S-malic acid, used by Johnson, gave the best yield at 30% overall to Corey

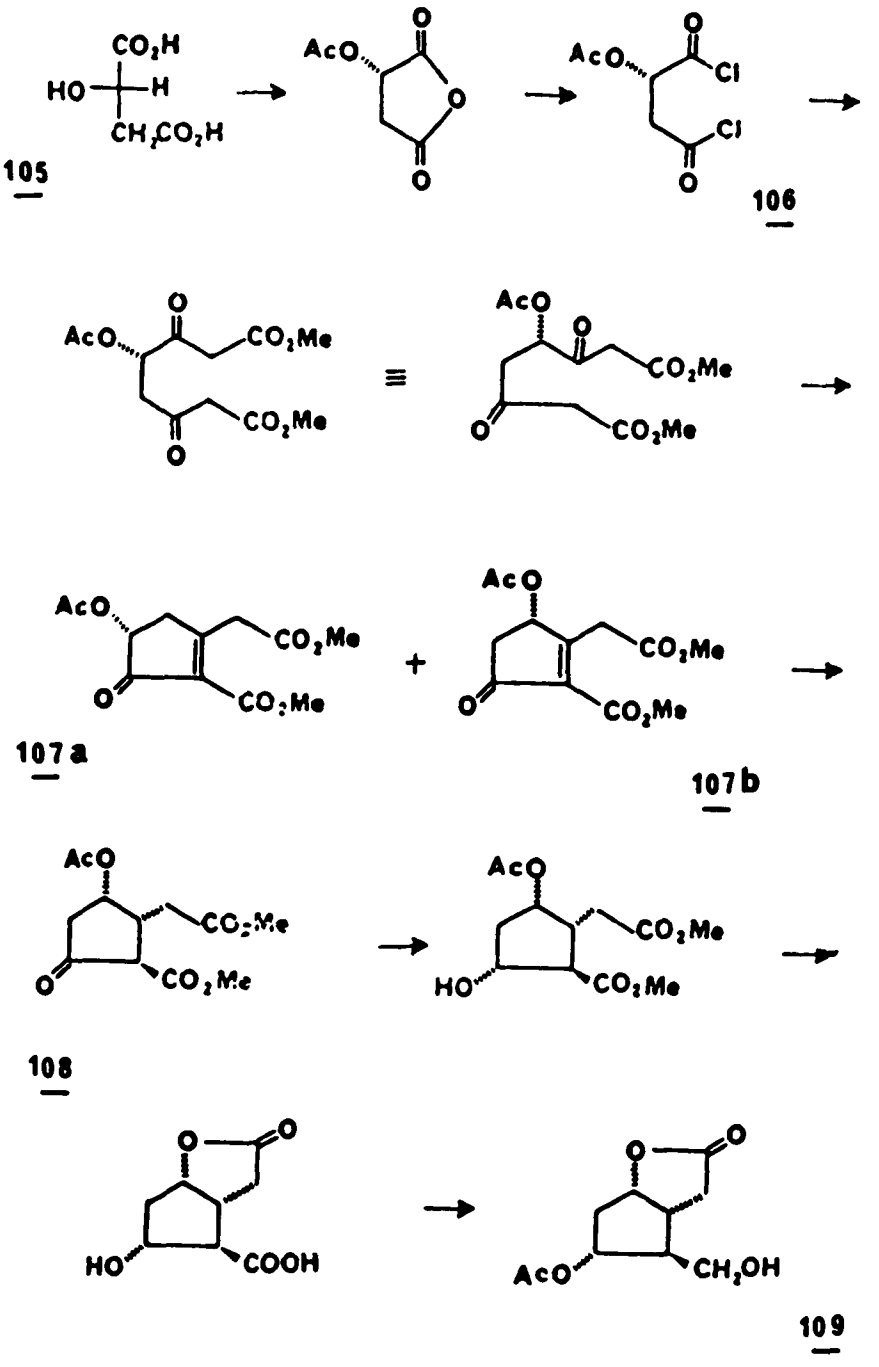
lactone aldehyde[82].

Johnson and his colleagues[82] reported a successful Corey alcohol synthesis from S-(-)-malic acid. S-(-)malic acid 105 was treated with acetyl chloride and afforded S-(-)-2-acetoxy succinic anhydride, which was converted to the corresponding succinyl chloride 106 in 80% overall yield by refluxing with dichloromethyl ether in presence of zinc chloride as catalyst. Alkylation of acid chloride 106 was achieved by treating it with 5 eq. of the dianion of methyl hydrogen malonate (derived from methyl hydrogen malonate and isopropyl magnesium bromide) at 0° in tetrahydrofuran. The product, (-)-4(s)-acetoxy 3,6-dioxosuberate, isolated as an unstable oil in 70% yield, was then subjected to Dieckmann cyclization with a buffer (triethanolamine/triethanolamine hydrochloride) at pH 8.5 . The cyclization was completed in 30 minutes and gave a mixture of cyclopentenones 107a and 107b.

The major product, 107b, was purified by direct crystallization (50% overall yield from 106). Catalytic hydrogenation (5% $Pd/BaSO_4$) afforded the cyclopentanone 108 in 95% yield. Sodium borohydride reduction of 108 followed by hydrolysis (potassium hydroxide/methanol) and acidification afforded the lactone-acid in 69% overall yield from 108. After protection of the hydroxyl group as an acetate (100%), the free carbonyl group was converted to the acid chloride using dichloromethyl ether in the presence of zinc chloride then reduced with sodium borohydride to give 109 in

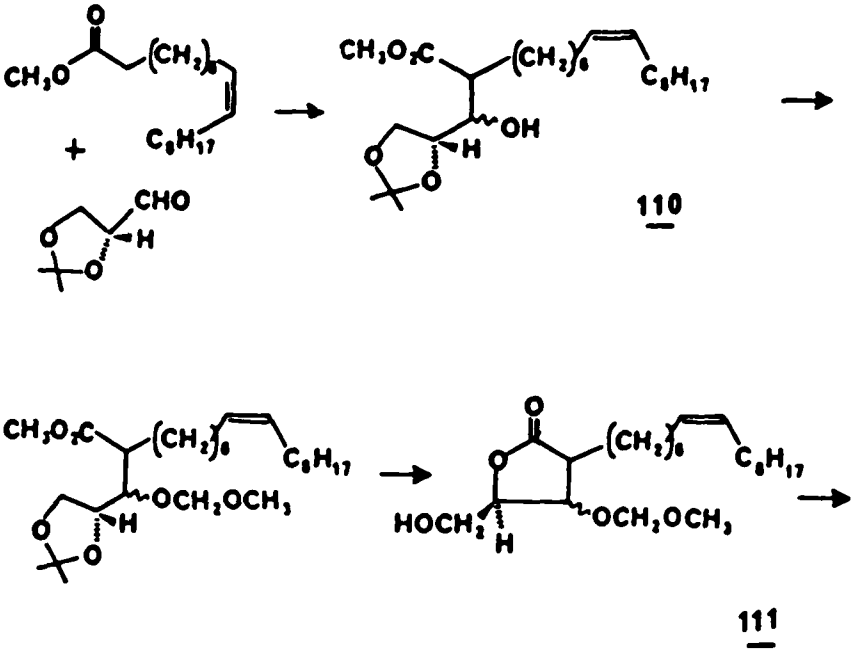
over 30% overall yield (See scheme 21).

Scheme 21 Johnson's Synthesis

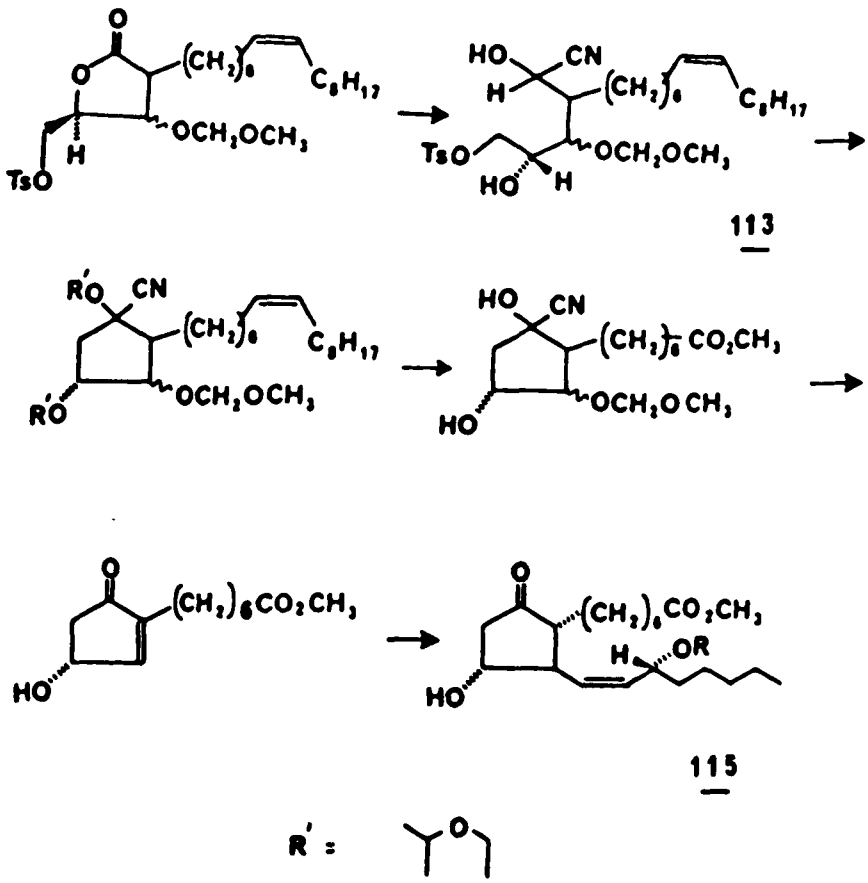


The Stork-Takahashi[79] team synthesized PGE_1 prostaglandins from the D-glyceraldehyde, methyl oleate being the choice for constructing the C-1, C-9 section. The rest of the synthesis was accomplished by an efficient means of kinetic resolution. Protection of the secondary hydroxyl group of 110 followed by hydrolysis and lactonization gave 111. Cyanohydrin 113 was formed by conversion of the lactol obtained from 112. Refluxing with base then gave the cyclopentane ring of 114. Conjugate addition of a pre-resolved lower side chain completed the synthesis of optically active synthon 115, which led to PGE_1 (see scheme 22).

Scheme 22 Stork-Takahashi Synthesis



(cont'd scheme 22)

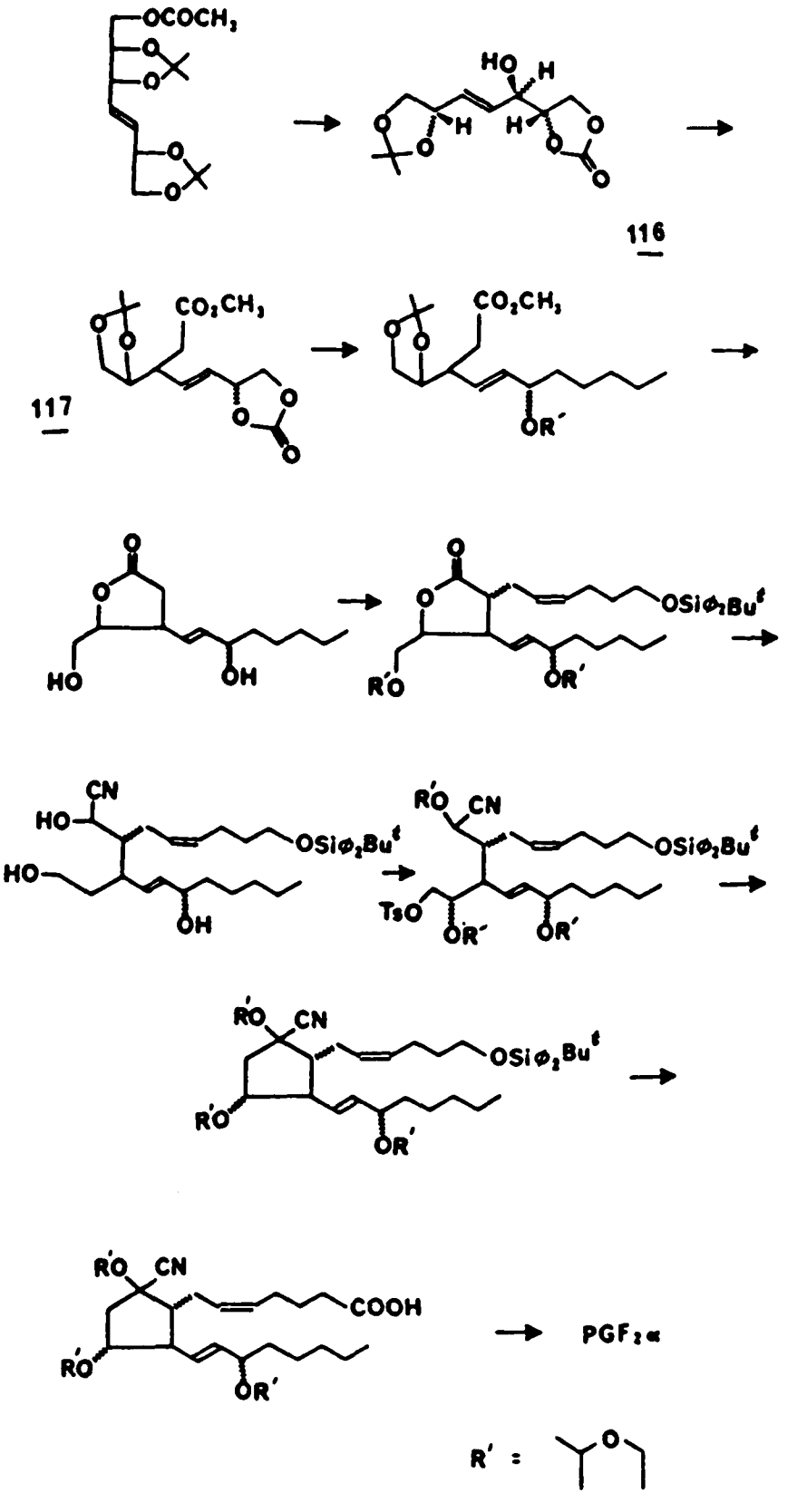


112 113 114 115

R' =

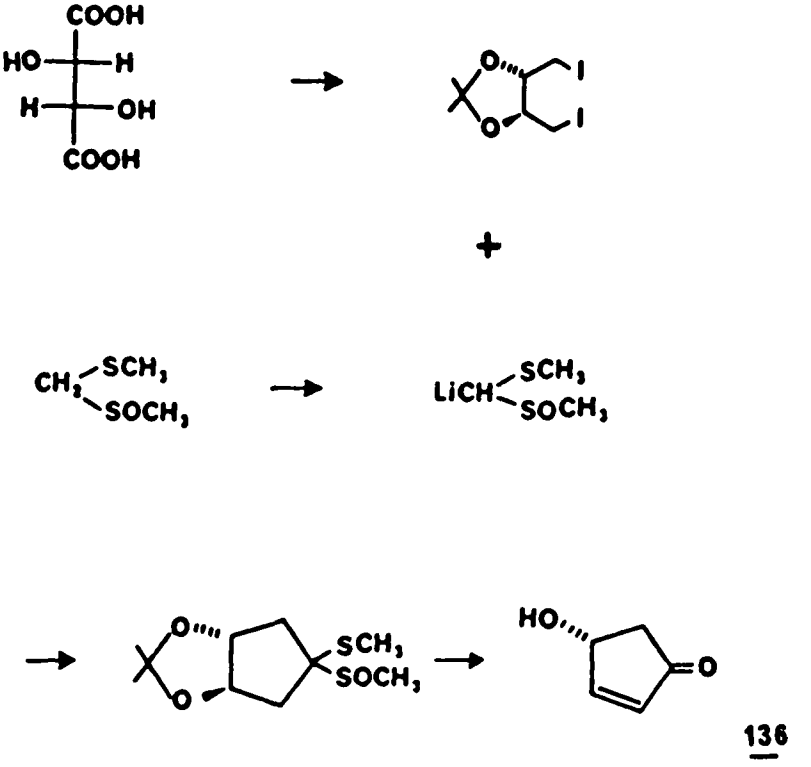
Stork[80] used a similar strategy in forming a cyanohydrin of a precursor prepared from D-glucose. A key step involved chirality transfer using the orthoester- Claisen rearrangement (116 to 117) to construct the allylic alcohol of the C_{16}-C_{20} side chain. Chain extension, lactone formation, tosylation, reduction and cyanohydrin formation led to cyclization and eventually to $PGF_{2\alpha}$ (See scheme 23).

Scheme 23 Stork Synthesis



Tartaric acid was also used as a precursor in the synthesis of natural series prostaglandins. Ogura and his co-workers[81] converted tartaric acid isomers to cyclopentenone 136 in a manner similar to Stork's prostanoid synthesis from glucose and glyceraldehyde. The synthesis involved protection of the glycol moiety of D-tartaric acid with dimethoxypropane, reduction of both the carboxyl groups to alcohols, formation of tosylates and their displacement with iodide, to provid optically active 1,4-diiodo-2,3-isopropylidenedioxybutane in 42% yield. This was reacted with a lithio derivative of methylthiomethylsulfoxide followed by acid hydrolysis to give 4-(R)-hydroxy-2-cyclopentenone in 52.5% yield (see scheme 24).

Scheme 24 Ogura Tartaric Acid Synthesis



136

VI- Iridoids

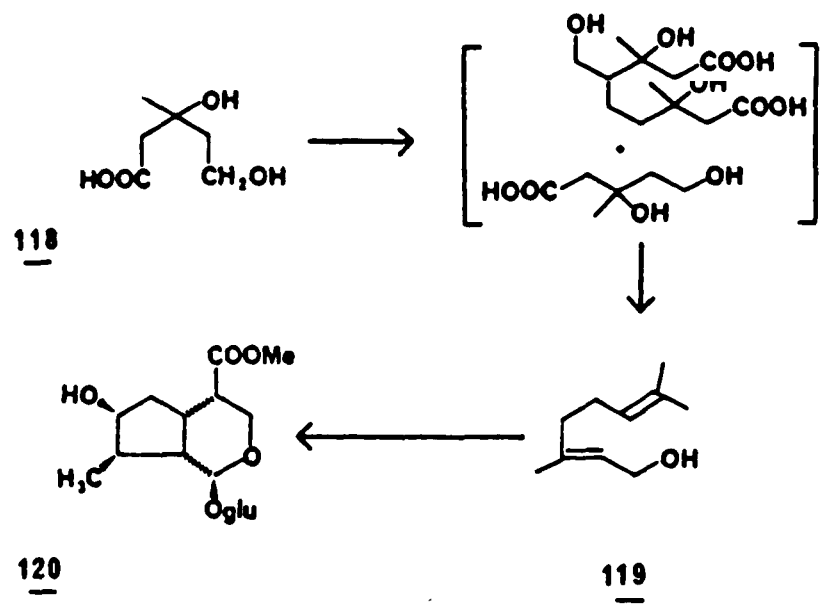
Iridoids were first brought to the attention of botanists and chemists by the intense blue color they form in plant extracts exposed to acidic conditions, due to the instability of the aglucone. Aglucones readily form under acidic conditions if accompanied by enzymatic degradation. Though iridoids were known to be glycosides since the early 1800's, actual structures weren't known until 1958. The first structural elucidation was performed on Plumieride in 1958[93] and mainly depended on chemical degradation and interconversions with known iridiod-like structures[90]. Definitive evidence for structural proofs originated from X-ray analysis by Abrahmson[91,92]. As the principle ring system became known, comparison of similar structures forced recognition of their wide occurence in plants.

Iridoids are generally found in nature in terrestrial plants, with young fresh plants having the highest content, although dried plants are also a source. Iridoids are isolated by extraction with hot water or organic solvents such as acetone, ethyl acetate or alcohol. The iridoids are chemically sensitive to acidic and basic conditions, and mold formation during isolation is also a problem due to the sugars also extracted. Chloroform or toluene added to the extracts has been a solution to the latter problem. Purification of the crude product depends on the iridoid involved.

One major source of iridiods are dicotyledonous trees and shrubs. Extraction from many different plant parts- leaves, stems, flowers, etc. using hot solvents followed by purification yields from 0.1 to 12% by weight of iridoids, but typically, for instance, 1.1-1.4% of loganin from strychnos nux vomica.

Radioactive labelling[84] has allowed biosynthetic pathways to be traced for the formation of iridoids, as shown below for loganin 120 . Two moles of mevalonic acid 118 are involved by way of geraniol 119, with additional carbons supplied by L-methionine and sodium acetate.

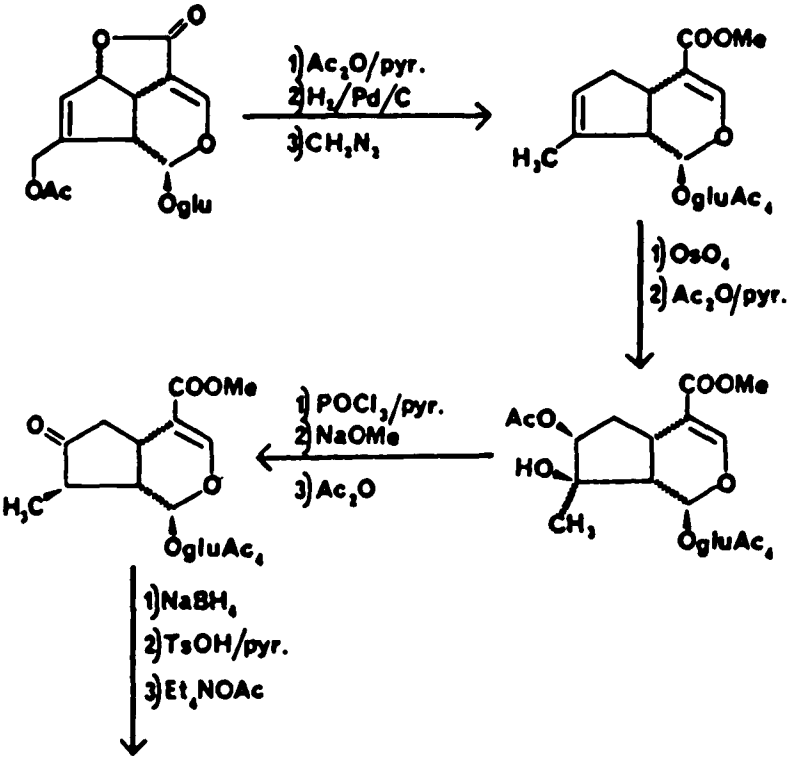
Scheme 25



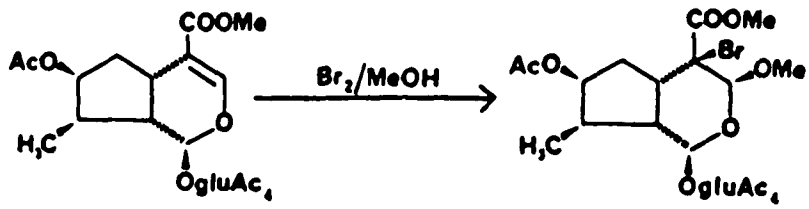
Iridoids are known to be alkaloid precursors and play an important role in plant defense. Although iridoids were investigated as antibiotics in the 1950's, they do not, at present, have any medical value[95]. Several studies have shown the iridoids as a class have the same absolute configuration. For instance asperuloside has been converted to loganin-pentaacetate[96] having an optical rotation identical to that obtained from naturally occuring loganin.

Scheme 26

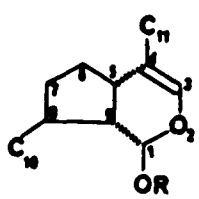
Conversion of Asperuloside to Loganin Derivative



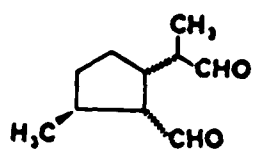
(Cont'd Scheme 26)



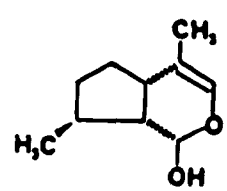
Iridoids were originally studied as a useful precursor for prostaglandin synthesis due to the common cyclopentano/pyran system 121 and the fact that prostaglandin C-8 and iridoid C-5 have the same absolute configuration[71]. Iridodial, 122, which exists as hemiacetal 123, is the parent compound of this family.



121

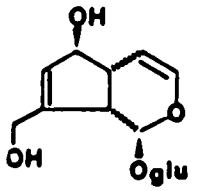


122

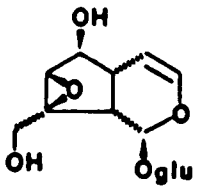


123

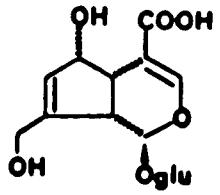
Given below are a few structural variations of the cyclopentane nucleus of some iridoids.



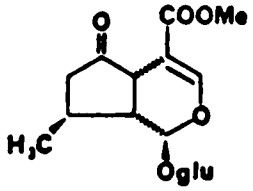
Aucubin



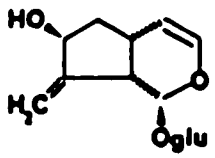
Catalpol



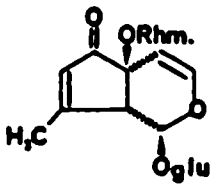
Daphylloside



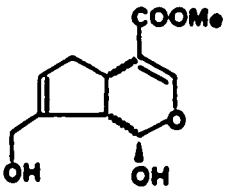
Verbenalin



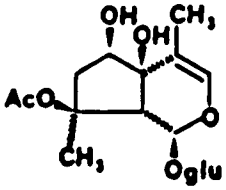
Antirrid



Teucardoside



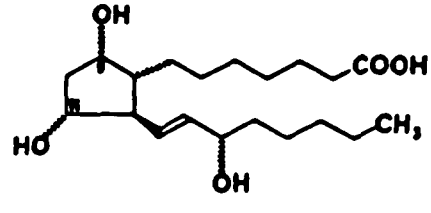
Genepin



Lamioside

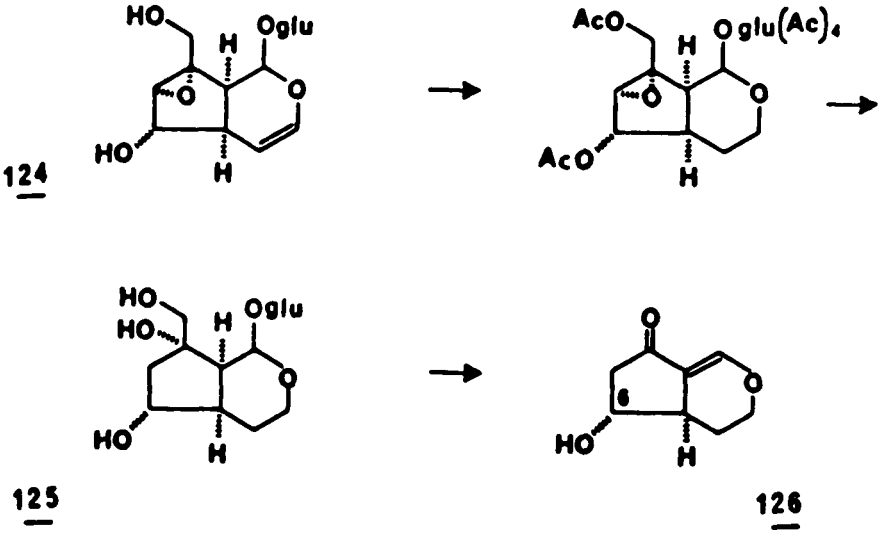
A shorter route to optically active prostaglandins may be possible from this class of natural material, and the last few years have seen an increase in interest in obtaining prostanoid synthons or prostaglandin analogs from iridoids, mainly aucubin, asperuloside and catalpol.

Catalpol 124 has been used as precursor for the preparation of optically active prostanoids. Catalpol was converted by Weinges et al.[85] into optically active tetrasubstituted cyclopentanone 126 a synthon suitable for making PGE's. The cyclopentanone nucleus of 126 is the same as that of the PGE series, and also has two side appendages in the oxidation states of alcohol and aldehyde, which could be used in the stepwise introduction of two side chains. Hexaacetyl dihydrocatalpol 124 was isolated in almost quantitative yield by acetylation and subsequent hydrogenation of catalpol. LAH reduction in tetrahydrofuran gave the triol 125, via a regioselective epoxide cleavage, which upon treatment with sodium periodate, gave 126 in 78% yield. The configuration at C-6 of 126 should be the same as that of catalpol and corresponds to the C-11 configuration of the prostaglandins.(see scheme 27)[85].



$PGF_{1\alpha}$

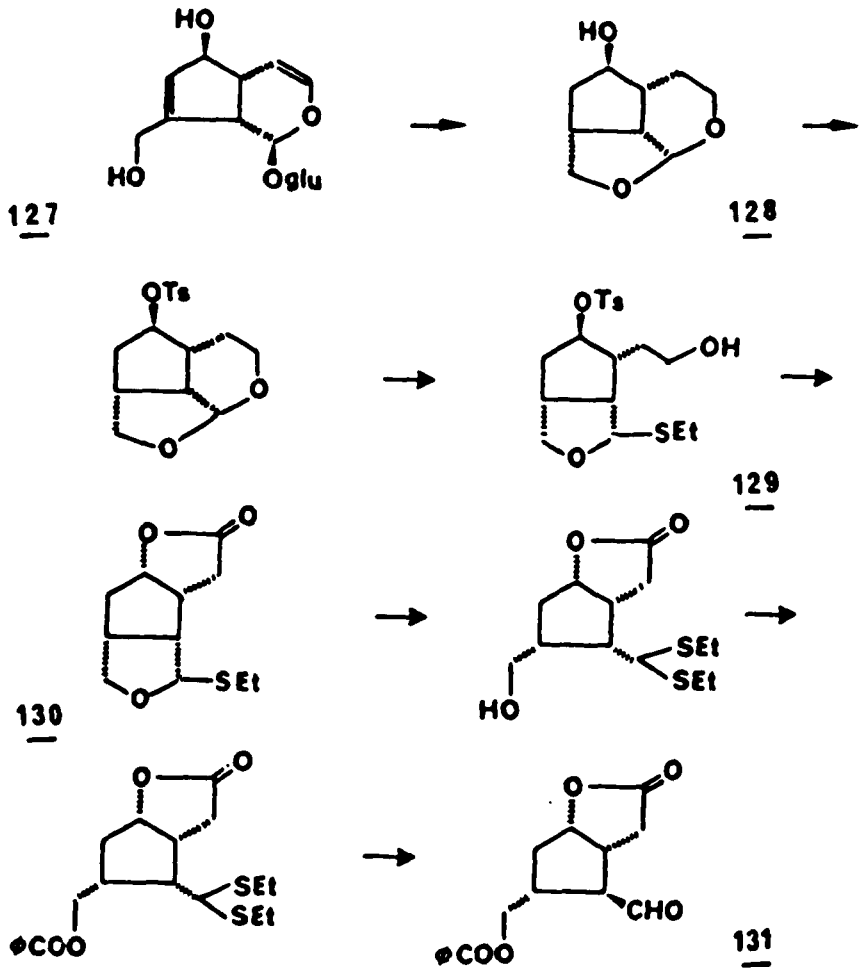
Scheme 27 Weinges Approach



124 125 126

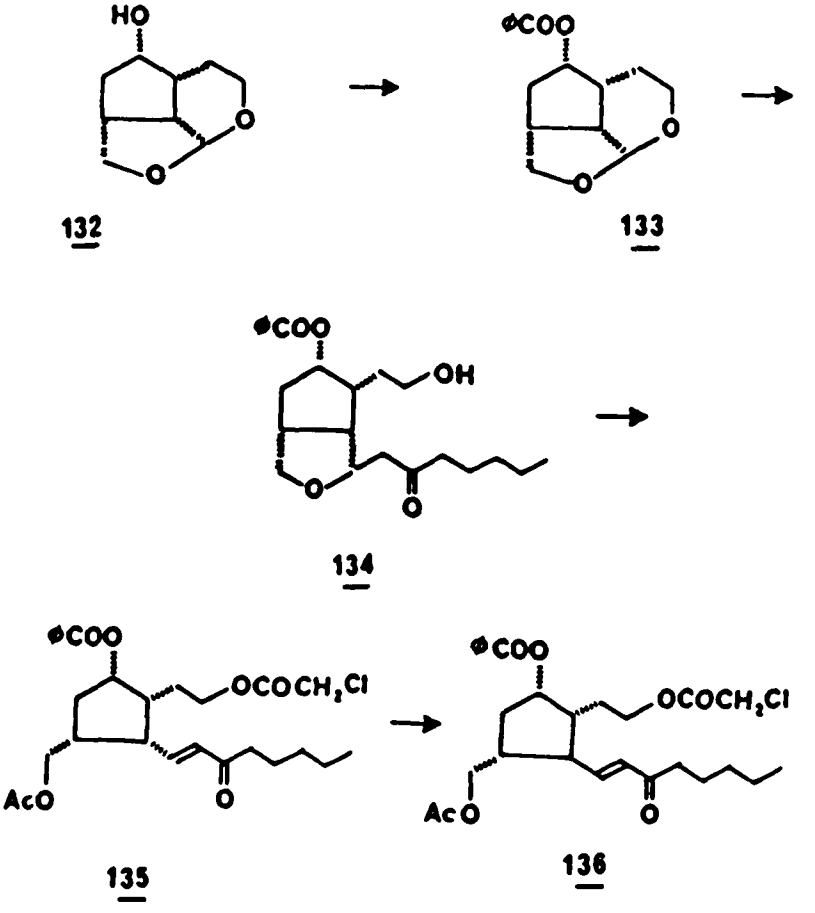
Ohno and his co-workers[86,87] have synthesized $PGF_{2\alpha}$ and 11-deoxy-11a-hydroxymethyl $PGF_{2\alpha}$ utilizing optically active iridoid aucubin 127. Tetrahydroanhydro-aucubigenin, 128, formed by hydrogenation and acid treatment of aucubin, was converted to tosylate 129. Cornforth oxidation of 129 gave the inverted lactone 130, which, after benzoylation and ring opening, resulted in a mixture of aldehydes. The more stable isomer 131 is a homolog of the Corey aldehyde, and was eventually converted into $PGF_{2\alpha}$ (see scheme 28).

Scheme 28 Ohno Approach



An alternate approach[67] inverted the free hydroxyl group of tetrahydroanhydroaucubigenin 128 by first oxidation and then $LiAlH_4$ reduction. The resulting alcohol 132 was converted to its benzoate 133. Mukaiyama-like reaction with $TiCl_4$ and 2-acetoxy-1-heptene regiospecifically opened the six-membered ring and attached the 2-ketoheptyl side chain.

Treatment of 134 with chloroacetyl chloride followed by p-toluenesulfonic acid gave the enone 135 by retro Michael reaction and isomerized it to the more stable form 136. Reduction of the enone carbonyl, removal of the chloroacetyl group, and introduction of the C-8 acid chain by established procedures completed the conversion of aucubin to 11-deoxy-11a-hydroxymethyl $PGF_{2\alpha}$.



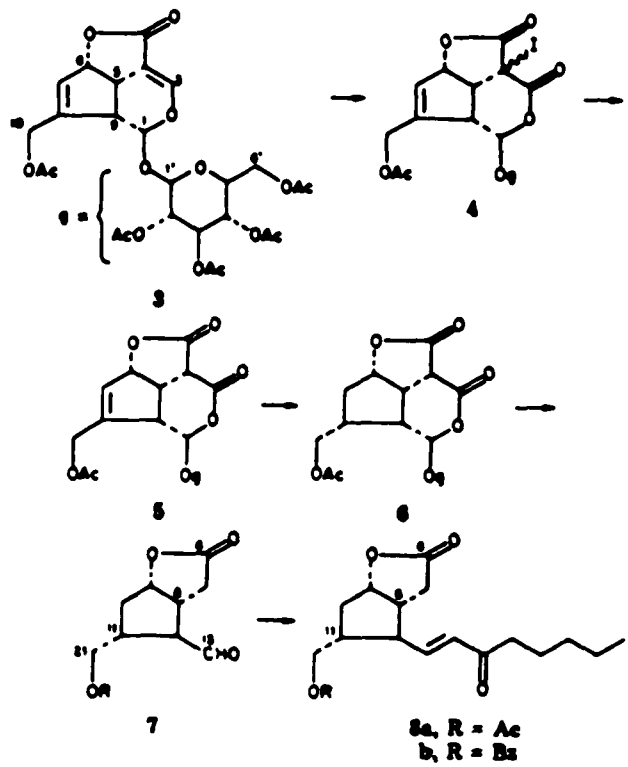
132 133 134 135 136

Berkowitz et al. in our laboratory, have attempted to generalize the use of iridoids for ring altered prostaglandins. Although it's difficult to manipulate

iridoids due to their acid/base sensitivity, this problem was overcome by either oxidation or reduction[38,39,40] to remove the enol double bond which is the origin of the instability of the aglucone. Several key prostaglandin intermediates and analogs have been prepared.

As shown in scheme (29) removal of C-3 of asperuloside by oxidation of the enol double bond followed by decarboxylation, and reduction of the cyclopentene double bond, gave a Corey type lactone suitable for further elaboration. Iridoid numbering is used if a glucose is attached, otherwise the prostaglandin numbering system is used throughout.

Scheme 29



Since the oxidation step is the most important of the synthesis, a brief discussion of the methods available for achieving this result follows. Specific methods we used can be seen in the the Results and Discussion section.

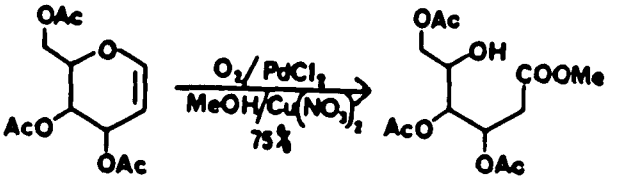
We are now confident that our work using optically active natural products may give high yields of many different intermediates, and analogues, of prostaglandin without need for optical resolution and without the need to develop a new strategy for each change in ring substitution.

VII- Conversion of Enol Ethers To Lactones

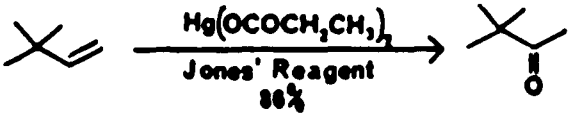
Schmid's preparation of aucubin hexaacetate lactone via the bromohydrin was the first procedure applied to the enol ether system of the iridoids. Work in our laboratory improved the yield substantially from initially approximately 20% over all, to 61% through use of the Dalton[99] bromohydrin procedure (NBS/wet DMSO). A two step conversion of aucubin hexaacetate to its lactone was developed in better than 80% yield[100] .

Other methods may also be applied: there is a report in the literature of a direct conversion of an enol ether to a lactone using pyridinium chlorochromate oxidation[101]. There are also several examples of oxidations of olefins which should be easily applicable to enol ethers. These

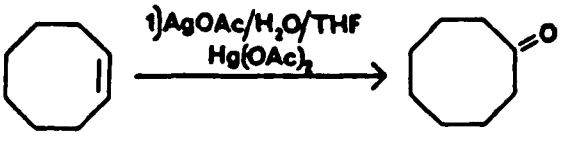
include a variation and modification of the Wacker oxidation developed by Gaudemer and Deslongchamps[102,103].



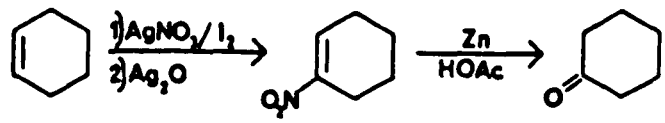
The Mercury (II) catalyzed oxidation with Jone's reagent as developed by Whitesides[107] may also be applicable.



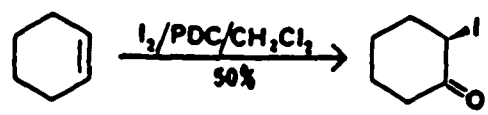
In addition, a method to produce a carbonyl rather than the usual hydroxyl by employing a variant of oxymercuration-demercuration is known, but the yield is not good (14%), as shown[109].



Other methods include the nitration of the alkene with iodine, silver oxide and silver nitrate to give the nitroalkene which will reduce to the ketone[112].



One final example of a two step conversion which was utilized in our laboratory is the formation of an alpha iodoketone in one step by Scettri et al.[113] as shown below. Zinc and acetic acid reduction may then be used to complete the conversion.

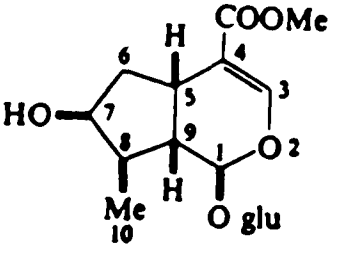


With such a considerable number of methods which might accomplish the conversion of the enol ether system of the iridoids to a lactone, the prospects for finding a method applicable to the majority of iridoids seems promising.

VIII- RESULTS & DISCUSSION

Introduction:

Work in this laboratory has resulted in the conversion of aucubin[100] and asperuloside[39] into prostaglandin analogs. Here we continue our interest in iridiod precursors to prostaglandins with loganin 1. The iridoid glucoside loganin occupies a central position in the biosynthesis[117] of Corynanthe[118], Aspidosperma[118], Iboga[118], Ipecacuanha[119] and Cinchona[119] groups of indole alkaloids Evidence indicates that loganin becomes the "C-9, C-10 " non-tryptamine moiety incorporated into the skeleton of these alkaloids. Tracer experiments also show that loganin is a biogenetic precursor of a growing number of iridoids[120], alkaloid glucosides[118], and monoterpene alkaloids[121]; additionlly, loganin is a potential precursor of the biogentically important substance secologanin[121].



1

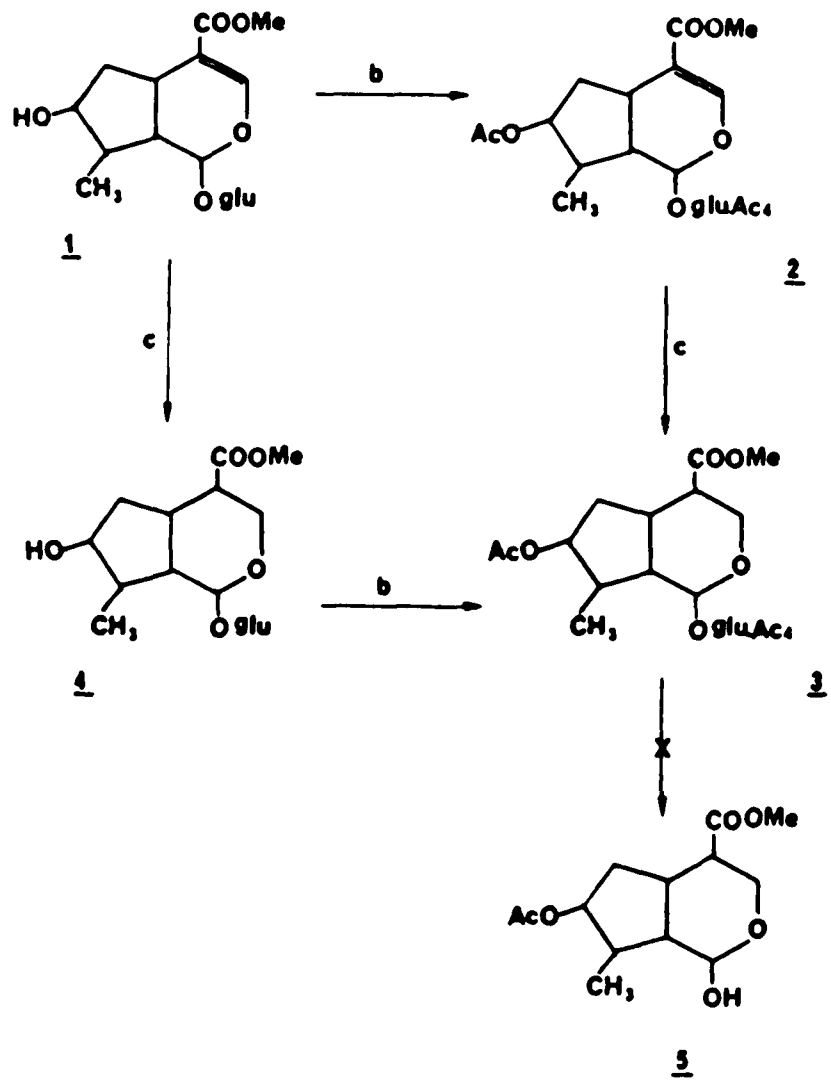
The Structure of Loganin

Loganin was first isolated from the fruit pulp of Strychnos nux Vomica[122]. It occurs in other strychnos species as well as in the water plant Menyanthes trifoliata and in Vinca rosa[118]. More recently, loganin has been detected in various species of Gentiana (Gentianaceae[120]), Hydrangea (Saxifragaceae[123]), Lonicera (Caprifoliaceae[123]), Mytragyna (Rubiaceae[124]), and Swertia (Gentianaceae[124]). Thus, loganin appears to be an important building block in much of the plant world.

The structure and stereochemistry of loganin have been the subject of many reports since it's discovery in 1884 by Dunstan and Short[122]. The correct structure was postulated by Wolinsky[12] in 1961, but the structure and stereochemistry were not firmly established until 1968 when three groups[119] independently announced corroborating evidence for it's absolute structure. This structure has since been confirmed by X-ray analysis[125], by the partial synthesis of Inouye[120], and by the total synthesis of Buchi[126,127].

The first goal of our synthetic plan is outlined in Scheme I and makes use of the Wittig reaction on the hemiacetal 5 rather than the free aldehyde.

Scheme I



1 2 4 3 5

a- $CHCl_3$/MeOH: 4/1, reflux.

b- AC_2O/Pyr. , reflux.

c- H_2/PtO_2/AcOH.

Isolation of Loganin

Loganin was extracted from the fruit pulp of Strychnos nux-Vomica supplied from United Chemicals and Allied Products, 10, Clive Row, Calcutta, India (see experimental). The isolated pure loganin melted at 220-4°C (reported m.p. 222-3°C)[127], and exhibited identical spectral properties and an undepressed mixed melting point with loganin previously obtained from Prof. J.Bobbitt (U.Conn., Storrs).

The conversion of loganin 1 to loganin pentaacetate 2 took place in refluxing acetic anhydride/pyridine for 2 hours. After the workup the pentaacetate was purified by crystallization from (CH_2Cl_2/Et_2O:1/1) to afford white crystal with melting point 139-140°C, (lit.[127] m.p. 137-139°C). ^{1}HNMR, IR and TLC data were consistent with loganin pentaacetate.

Hydrogenation of Loganin And Pentaacetyl Loganin

Merz and Lehmann[135] reported that loganin undergoes an extremely slow hydrogenation. Several experiments carried out by Sheth[12] using Raney nickel, with or without pressure, proved ineffective. Palladium was similarly found inactive as a catalyst. However hydrogenation carried out in glacial acetic acid with platinum oxide as a catalyst

proceeded smoothly and was complete after approximately 3 hours at atmospheric pressure and room temperature[12]. An unusually, large amount of catalyst was needed to effect hydrogenation, the amount being 50% of the weight of the compound to be hydrogenated.

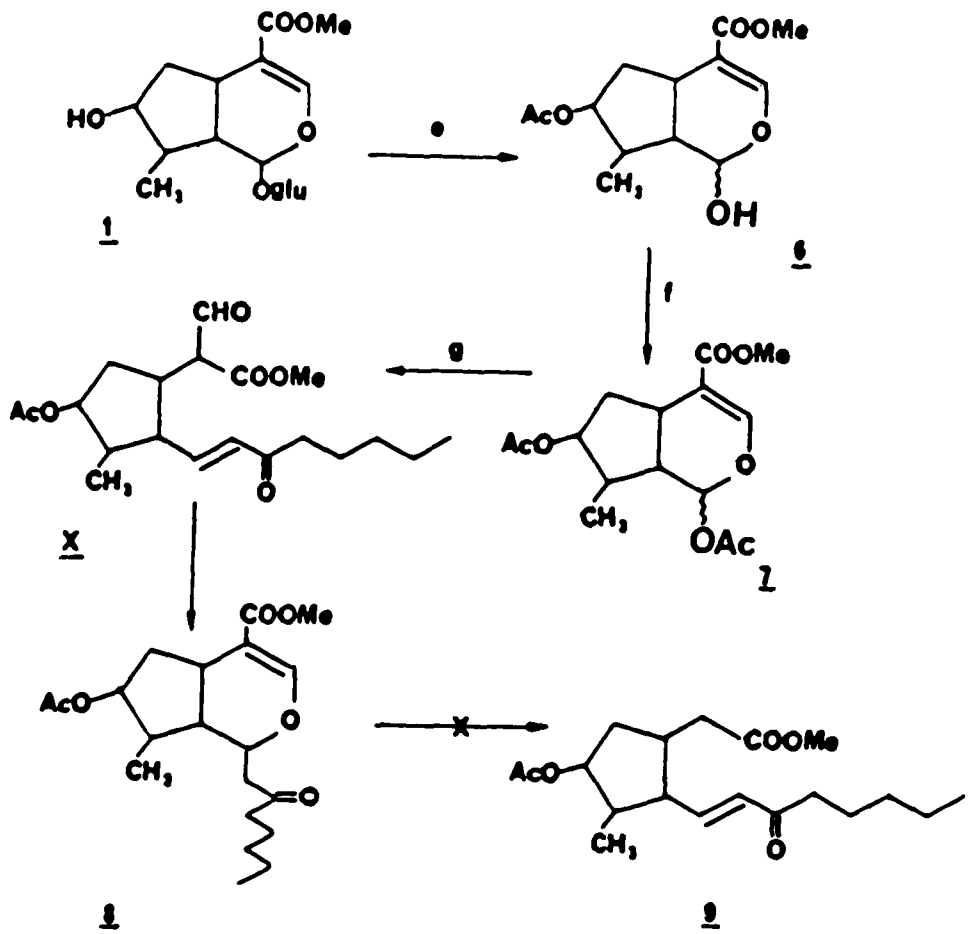
The conversion of loganin to dihydrologanin 4 and penta-acetyl loganin to dihydro-pentaacetyl loganin 3 was established in both cases by the loss of the 1660 cm^{-1} band in the IR, as well as the disappearance of the vinylic hydrogen at 7.20 in the ^{1}HNMR, elemental analysis and R_f comparisons.

We were able to obtain dihydrologanin pentaacetate 3 by two slightly different routes as shown in scheme (I): hydrogenation of loganin followed by acetylation gave an 84.2% overall yield, and acetylation of loganin followed by hydrogenation gave an 80.4% overall yield of the same product.

The next step to reach our goal was to cleave the glucoside linkage and produce the aglycone hemiacetal 5 in acceptable yield. Several experiments and variations gave discouraging results, and failing to obtain the desired hemiacetal 5, we chose an entirely different approach, using a Lewis acid as shown in Scheme (II).

using a Lewis acid as shown in Scheme (II).

Scheme II



e- $BF_3.Et_2O/Ac_2O$, rt.

f- AcOH/HCl/THF: 1/1/1, rt.

g- $NaH/DME/C_5H_{11}COCH_2P(O)(CH_3O)_2$.

Preparation of Diacetate

The diacetate 6 was obtained in 78% yield as a 3/2 mixture of epimers upon treatment of loganin directly with $BF_3.Et_2O$ in acetic anhydride at room temperature. We noticed that 20 minutes after the reaction started all of the loganin had been converted to loganin pentaacetate. Investigation of this reaction in other experiments showed that acetylation of loganin using boron trifloride etherate in acetic anhydride cleanly gave the loganin pentaacetate in almost quantitative yield (98%).

To obtain the diacetyl aglucone 6 in 78% yield, reaction must be completed in 3 to 4 days. Trials to shorten the time by slightly raising the temperature gradually to about 40°C to 50°C, resulted in polymerization and formation of a black tar. Also, a catalytic amount of boron trifluoride etherate was not enough, and experiments proved that $BF_3.Et_2O$ must be in excess.

Preparation of Aglucone Monoacetate.

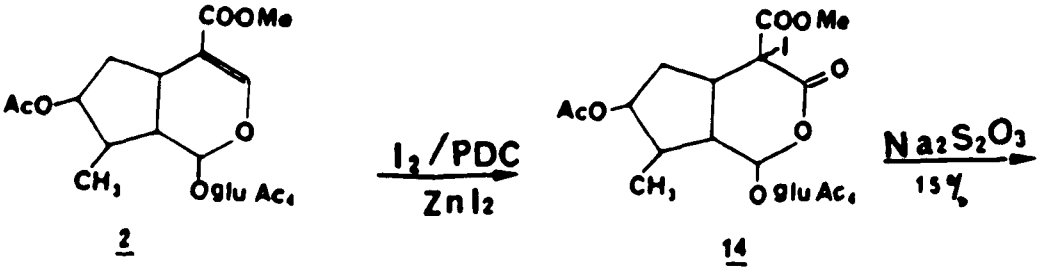
A varity of conditions were tried in the attempt to selectively hydrolyse the diacetate to monoacetate 7 :
1- Treatment of diacetyl aglucone 6 with THF/AcOH/H_2O (1/1/1) and stirring at room temperature for various reaction times. 2- Treatment with THF/HCl 3M (10/1) and silica gel at room temperature for different times. In all

experiments either the dihydroxy compound resulted either as the major product or in an almost equal amount with the desired aglucone monoacetate 7 (TLC). We finally discoverd that HCl/THF/AcOH (1/1/1) for 7 hour between 0-5°C, caused selective hydrolysis of the diacetate, and afforded the desired product 7 in 88% yield after flash chromatography as a mixture of epimeric hemiacetals.

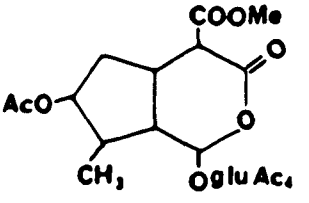
Our last step, to prepare the enone via Wadsworth Emmons reaction of the aglucone 7, however, gave only 8, the product of subsequent intramolecular Michael addition of intermediate X as shown in scheme (II). Attempts to generate the desired enone 9 by acid catalysed retro-Michael reaction, as achieved by Ohno[134] with an analog prepared from aucubin, was not successful.

The following are some of the variations tried:
1- Treatment of Michael adduct 8 with P-TSOH in toluene at 110°C for 18 hour ; 2- Treatment with P-TSOH/DMF/NaCl, at 110°C ; 3- Treatment with boron triflouride etherate in acetic anhydride ; 4- Treatment with TMSCl and NaI/CH_3CN at room temperature to 90°C. In all examples, either decomposition or no reaction took place.

Oxidation of an iridoid enol ether to a lactone has been accomplished several times, in particular by method of D'Ascoli et al[39,113] . This procedure converted loganin to the corresponding lactone in 55% yield, as shown below:

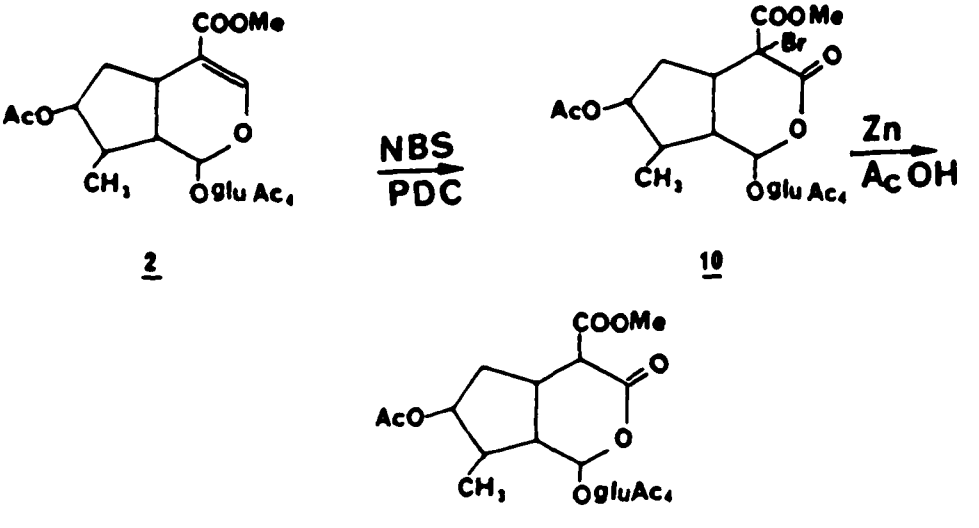


2 14



11

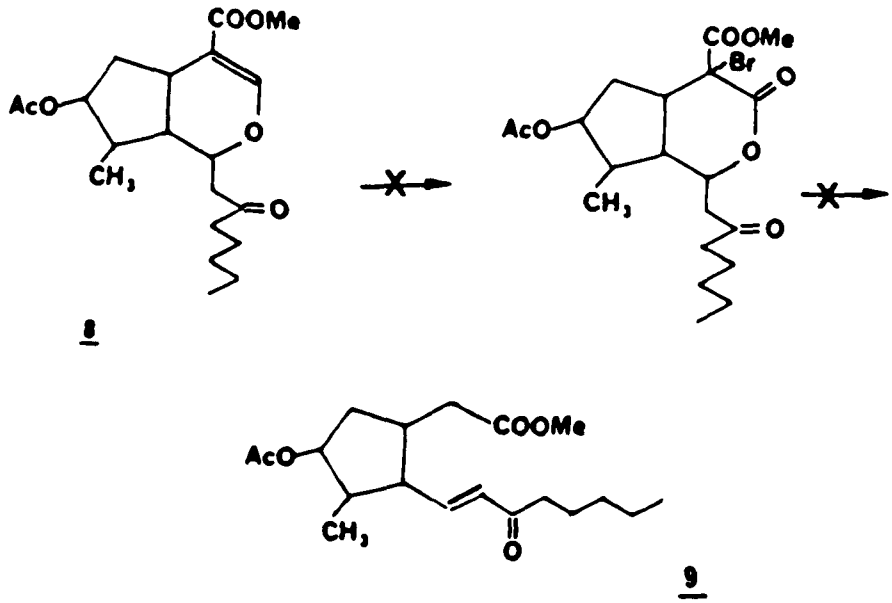
On the other hand, we found that substitution of NBS for I_2 and reduction with Zn/AcOH rather than thiosulfate improved the yield to 83% .



2 10

11

This successful reaction encouraged us to bromo-lactonize the Michael adduct 8 itself using NBS/PDC/CH_2Cl_2 because if this reaction worked, we would obtain the desired product 9, especially if decarboxylation occurred in the same pot after retro Michael-adduct lactone opening as shown :

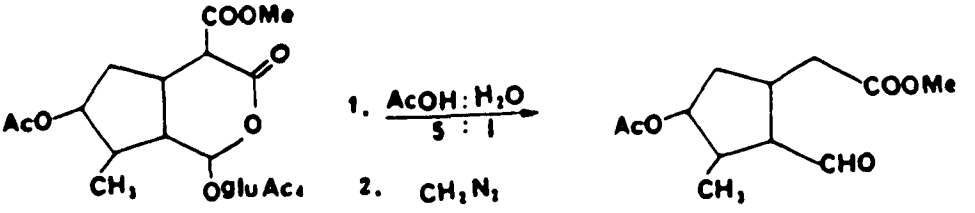


8

9

This reaction however, did not proceed as cleanly as the oxidation of loganin pentaacetate 2. It seems that the bromo-lactone shown above is not stable and breaks down to other products on treatment with Zn/AcOH (3 spots on TLC; some times 4 spots with different solvent systems).

An alternative approach is to produce the carbomethoxy-aldehyde 13 by hydrolysis-decarboxylation of loganin penta-acetate lactone 11.

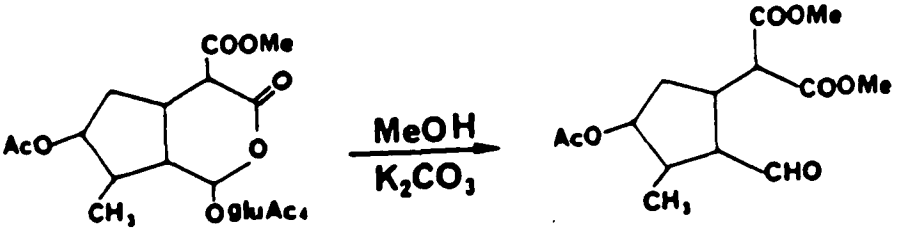


11 13

Hydrolysis-Dicarboxylation of LPA-Lactone

Following are some of the variations tried:

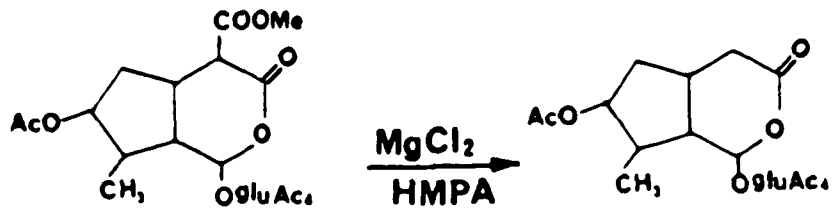
1) Base hydrolysis gave aldehyde 16.



11 16

The above reaction went smoothly at room temperature to give the malonic ester aldehyde 16 in 89% yield, in 2 hours.

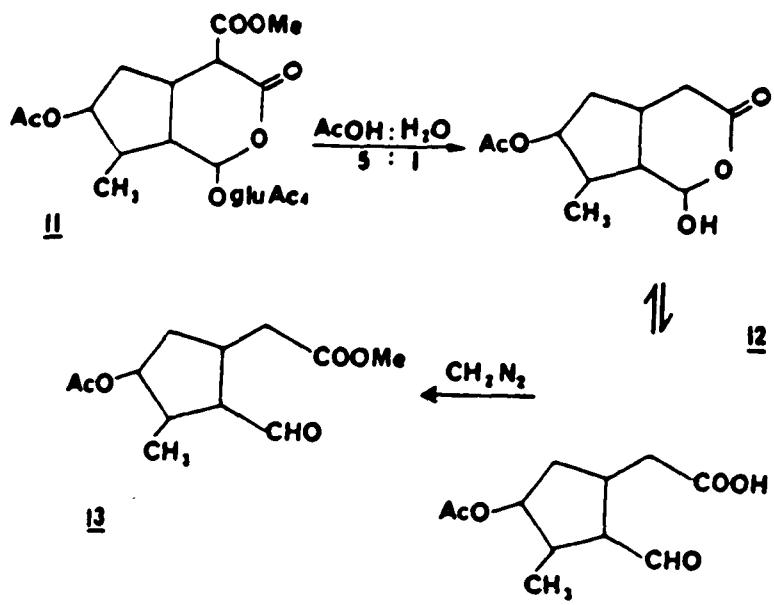
2) Decarboxylation of the lactone directly with HMPA/MgCl2 gave a lactone 15 similar to the lactone obtained by Bonini et al.[71] :



11 15

The reaction mixture was stirred for only one hour at 145-50°C, and after workup and purification of the desired product on the Chromatotron (using Hex:EtOAC/3/1), gave a 69% yield of white solid 15 with m.p. 137-140°C.

3) Ring opening and glucose cleavage with decarboxylation of 11 was accomplished in one pot with 80% aqueous acetic acid at 120-125°C in 36 hours.



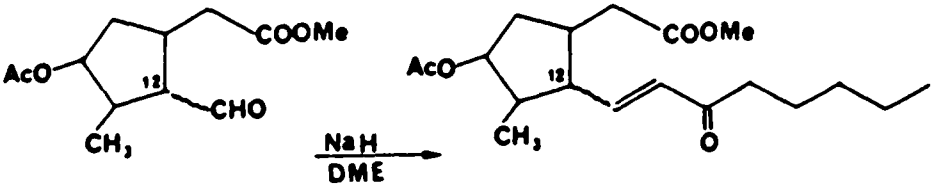
11 12 13

After reaction, the crude product showed acidic as well as aldehydic protons in the ^{1}HNMR. Therefore, the crude mixture, without further purification, was treated with diazomethane in ether at room temperature. Purification of the product on the Chromatotron (using, Hex/Et$_2$OAc:3/1) gave the desired carbomethoxy-aldehyde 13, in 67% yield.

The aldehyde 13 was shown by ^{1}HNMR and HPLC to be a mixture of two stereoisomers (2:1) at C-12. Due to the fact, that next step planned was Wadsworth Emmons reaction of the aldehyde-ester, which were epimerizing conditions as well, we went directly to the next step with the mixture of two isomers.

Preparation of The Enone 9

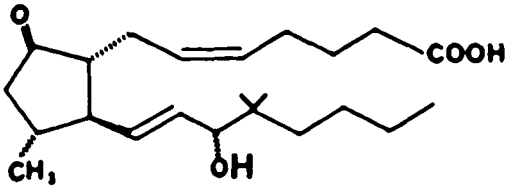
The reaction of the aldehyde 13 with the sodium derivative of 2-oxoheptyl-phosphonate was done as previously described by Corey[50], except that granules of sodium hydride were used instead of a dispersion in mineral oil. This afforded 9 in a good yield (89%).



13 9

The enone 9 showed the appropriate coupling constant (15 Hz) for a trans double bond. The enone was obtained as two isomers at C-12. ^{1}HNMR (200 MHz) and HPLC showed a 88:12 ratio of Wittig adduct 9.

At that time we became aware that Hoffman LaRoche had developed a new antiulcer agent(A)[110] with the following structure:



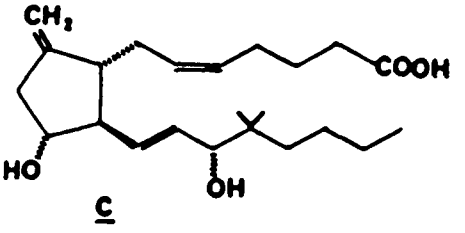
A

(11-R)-11-deoxy-11,16,16-tri-methyl-PGE2

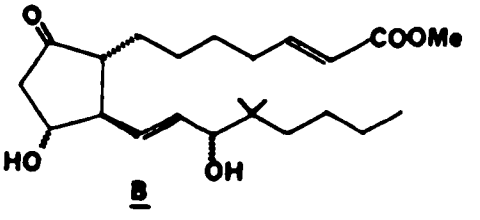
The potential utility of this compound is treatment of peptic ulcers and protection of gastric musoca. It's CAS Registry No. is [6990-72-7] and trade name is RO21-6937. At present it is being developed for the market at the Hoffman La-Roche unit in Japan.

Prostaglandin analogues have shown a variety of useful pharmacological advantages, including selectivity of action, increased potency for a given biological response, prolongation of the duration of action of the short-lived, naturally occuring prostanoids, enhanced chemical stability, and simpler structures which still maintain desirable a biological profile[136,137]. Since the metabolic oxidation effected by C-15 prostaglandin dehydrogenase (15-PGDH) is very rapid, numerous analogues that contain alkyl

substituents at or near C-15 have been synthesized, eg. (B)[111] which was developed by Ohno (Osaka, Japan and known in the market as gemeprost. It's clinical utility is termination of pregnancies and cervical dilation. Also (C)[116] is being developed by UpJohn Company and it's trade name is meteneprost; the potential utility of this compound is induction of menstruation and cervical dilation.



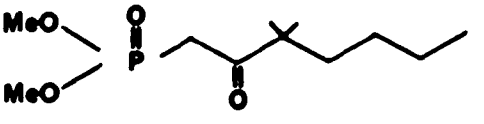
C



B

Such analogues are resistant or less susceptible to the action of the dehydrogenase. The C-2, C-3 double bond in structure (B) is also believed to significantly retard it's oxidation[138,139].

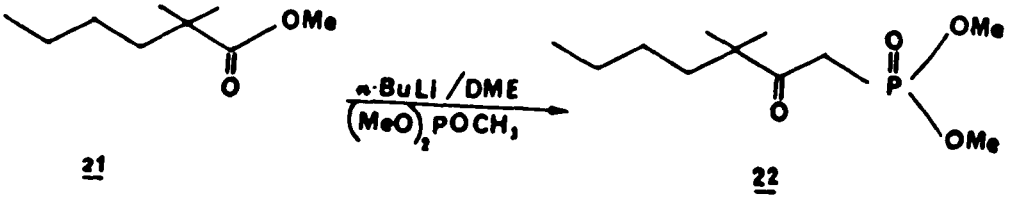
In order to determine whether the loganin-derived analog might have similar medicinal properties, we decided to try to append the gem-dimethyl substituted side chain. This required the corresponding Wittig reagent 22 shown below:



22

dimethyl(2-oxo-3,3-dimethyl-heptyl)-phosphonate

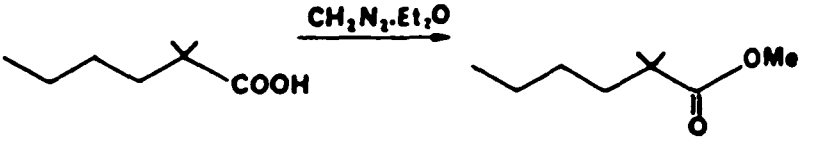
We accomplished the preparation of the Wittig reagent 22 in 76% yield via acylation of the dimethyl methylphosphonate anion with gem-dimethyl ester 21. The anion was generated with 2 equivalents of butyl lithium in dry dimethylformamide at -78°C by the procedure used by Corey[128].



21 22

Preparation of Methyl 2,2-Dimethylhexanoate

The gem-dimethyl ester 21 was obtained easily, in 80% yield, by a normal esterification of the corresponding 2,2-dimethyl hexanoic acid 20, using methyl orthoformate in dry methanol and a catalytic amount of acetyl chloride at room temperature[129].

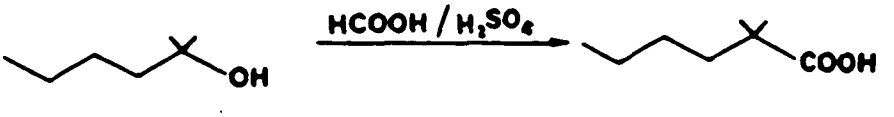


20 21

Although the diazomethane procedure[130] was superior, the disadvantages of it's hazardous properties prohibited its use for large scale experiments.

Preparation of 2,2-dimethyl hexanoic Acid

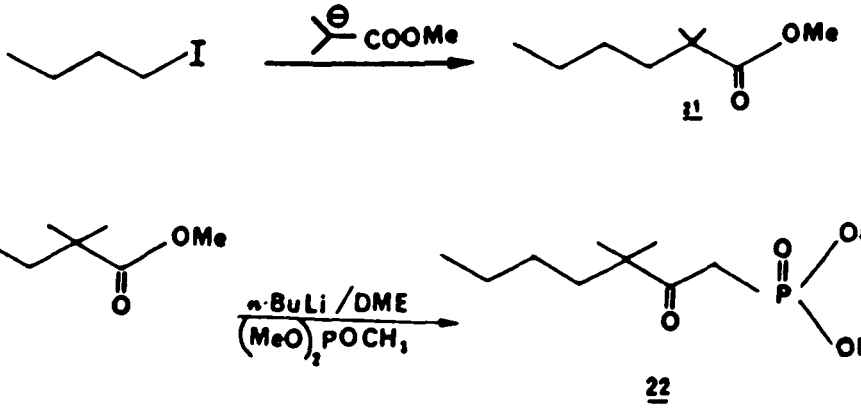
We considered preparation of 2,2-dimethyl hexanoic acid 20 via hydrolysis of the corrosponding nitrile compound which, however we were unable to prepare from the tertiary alcohol 19 using the procedure of Untch et al.[131]. Our attention was then directed to the carboxylation procedure[132] using formic acid and sulfuric acid at room temperature. An initial yield of 45-50% was improved to 70% by using a catalytic amount of cuprous oxide[133].



19 20

The tertiary alcohol 19 was prepared from butyl-magnesium bromide and dry acetone by the well known Grignard procedure in 80% yield.

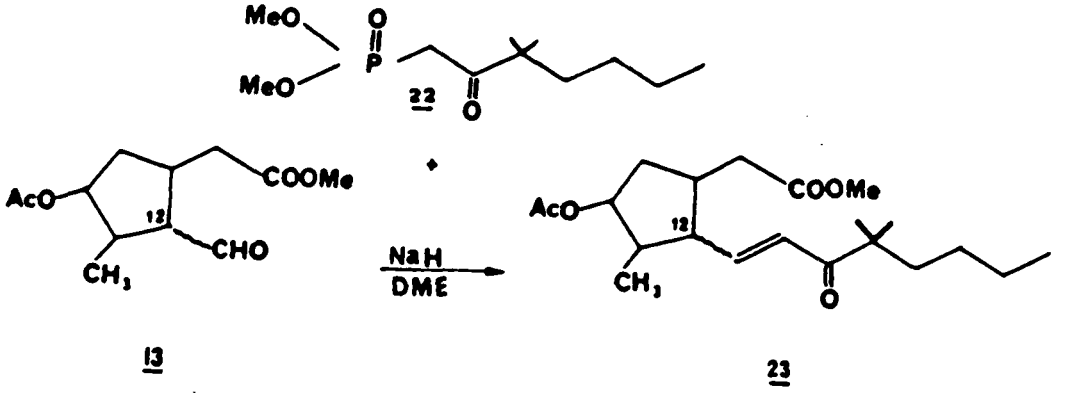
We also looked at the following two step reaction:



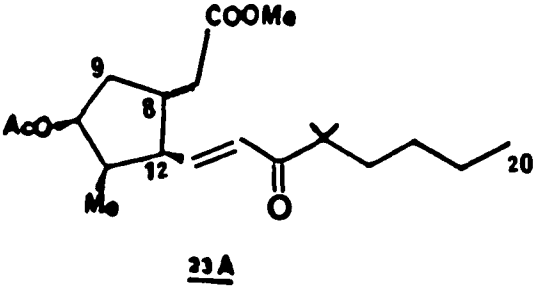
Alkylation of the isobutyrate anion using butyl bromide did not take place, but butyl iodide readily gave 21 in 89% yield using the procedure of Rathke[135].

Preparation of The Enone With Gem-dimethyl

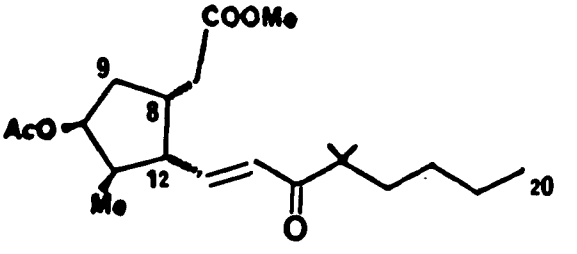
Wadsworth Emmons reaction of the aldehyde ester 13 with the anion of dimethyl 2-oxo-3,3-dimethylheptylphosphanate was done using sodium hydride in dry DME and gave 81% of an 8:1 mixture of two epimeric enones 23A and 23B respectively.



Separation of the epimers was cleanly accomplished by HPLC (Hex/EtOAc: 12/1), and both isomers were submitted to high field COSY analysis including J maps. The following ^{1}HNMR (400 MHz) evidence along with literature data leads us to conclude that the major isomer is the desired prostanoid-like trans epimer.



23A



23B

Stereochemistry Assignment

The ^{1}HNMR (400 MHz) for the compound 23A, a major product of the Emmons-Horner reaction gave, chemical shift, multiplicity and J values as follows:

The doublet at 6.35 with a coupling constant of J=15.0 is assignable to the vinyl proton at C-14, and confirmed the presence of a trans double bond. The doublet of doublets at 6.80 is assigned to the C-13 proton with coupling constants of $J_{13,14}$=15.0 , $J_{12,13}$=8.5 . Coupling constants were derived from an examination of the 400 MHz spectrum, including a COSY experiment (Appx. q & r), and proton assignments are given as shown above.

Literature data (as sumarized, in the following table) indicate that, for trans -15-Keto and 15-S hydroxy analogues with the - configuration for the omega side chain, $J_{12,13}$ values fall within the range of 7.5-9.0 Hz[87,139,140,142.], while for the configuration the J values are in the range of 10.5-11.0 Hz[87,142].

By comparison our data show that 23A falls in the category of a -side chain configuration for these analogues, although one may argue that a difference of only 1.5 to 2.0 Hz may not be enough to draw such a conclusion. However, the argument may also be made that $J_{12,13}$ values for the -configurations are always higher than for the -isomers.

In fact, the minor isomer, 23B, exhibits a doublet at 6.40 with (J=15.0) assignable to the C-14 hydrogen, and doublet of doublets at 6.65 with a $J_{13,14}$=15.0 , $J_{12,13}$=9.9 values. Again the trend is in agreement with the literature data, and this further confirms the -configuration for the side chain for compound 23B, i.e. the C-8 and C-12 protons are cis to each other.

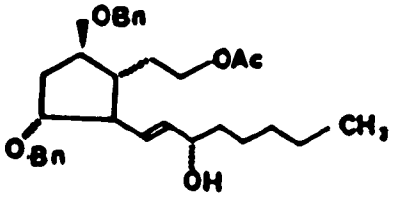
It would have been perhaps better to have been able to assign the stereochemistry based upon $J_{8,12}$; however, the C-8 protons of both 23A and 23B have almost the same chemical shifts as at least 5 other protons, and as a result, it is difficult to assign specific $J_{8,12}$ values for such compounds. This may be the reason that $J_{8,12}$ is seldom reported in literature[87,142].

Table #1

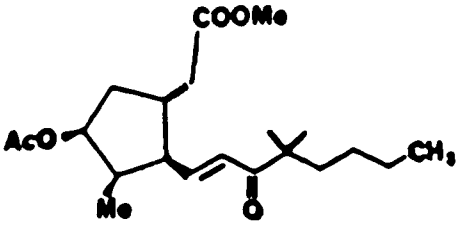
Literature Data

		Hz	δ	δ	
15-Keto					
Trans	(β)	J(12,13)	H13	H14	Ref.
		8.0	6.69	6.20	(87)
		8.8	6.73	6.17	(142)
		8.6	6.61	6.18	(39)
Cis	(α)	11.0	7.03	6.19	(87)
		10.6	6.76	6.18	(142)
15-S Hydroxy					
		8.1	5.54	5.59	(139)
Trans	(β)	7.7	5.53	5.67	(139)
		8.3	5.59	5.69	(140)
		7.5	5.42	5.47	(141)
		8.1	5.49	5.59	(142)
		8.0	5.52	5.45	(143)
		7.5	5.42	5.47	(136)
Cis	(α)	9.8	5.39	5.56	(141)
		---	5.67	5.55	(142)
Our Data					
Cis	(α)	9.9	6.65	6.40	23B
Trans	(β)	8.5	6.80	6.35	23A

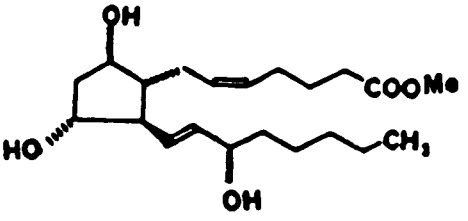
Structures & References Indicated In Table #1



(142)



23A



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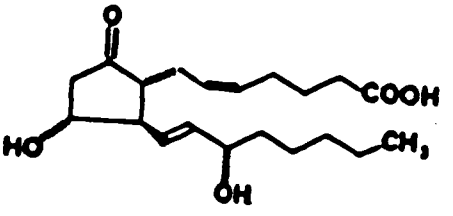

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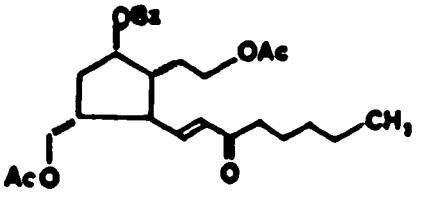

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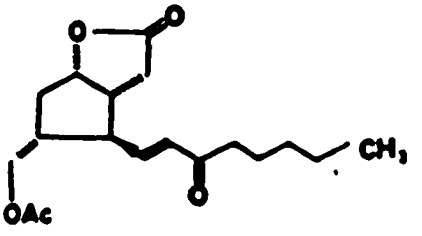

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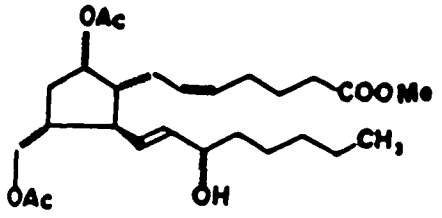

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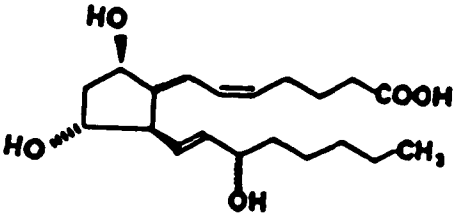


(136)

Abstract, COSY Experiment

Trans Isomer 23 A

observed		coupled to														
δ	assed	7A	7B	8	9A	9B	10	11	12	13	14	17A	17B	18	19	20
2.36	7A		15.0	5.3												
2.24	7B	15.2		8.2												
2.43	8	•	•		•	•										
1.67	9A			8.2		14.5	6.3									
2.11-2.03	9B			•	•		•									
5.17	10				•	•		•								
2.43	11						•		•							
2.43	12							•		•						
6.82	13								8.8		15.0					
6.40	14									15.2						
1.49	17A												•	7.4		
1.49	17B											•		9.4		
1.05-1.15	18											•	•		•	
1.24	19													7.4		7.0
0.84	20														7.2	
1.09	21															
1.09	22															
0.81	23							6.3								
2.04	24															

Abstract, COSEY Experiment

Cis Isomer 23 B

observed		coupled to														
&	assd	7A	7B	8	9A	9B	10	11	12	13	14	17A	17B	18	19	20
2.34	7A		15.7	6.8												
2.17	7B	15.6		9.0												
2.83	8	•	•		•	•										
1.69	9A			2.5												
1.69	9B			•	•		•									
5.22	10				•	•		•								
1.96-2.08	11						•		•							
2.62	12			•				•		9.8						
6.69	13								10.0		15.0					
6.46	14									15.2						
1.49	17A												•	•		
1.49	17B											•		•		
1.03-1.17	18											•	•			
1.23	19														•	6.4
0.84	20														6.4	
1.09	21															
1.09	22															
0.88	23							6.4								
2.03	24															

IX- EXPERIMENTAL

Melting points were determined in open capillaries using a Thomas- Hoover Uni-melt apparatus and are uncorrected. Routine proton spectra were recorded at 60 MHz on a Varian EM360 instrument. High field spectra were obtained at either 200 MHz (IBM-Bruker) or at 400 MHz (situated at Hunter College of the CUNY) as specified below. NMR data are reported in ppm downfield from Me_4Si, with the multiplicity (s,d,t,q,m), assignment and splitting con stants in parenthesis. Unless otherwise indicated, all spectra were determined using solutions in deuteriochloro-form containing Me_4Si as the internal standard.

Infrared spectra were taken with a Perkin- Elimer IR 598 and were calibrated against polystyrene film.

Silica gel thin-layer chromatography was performed using Machery-Nagel Sil N/HR UV250 precoated plastic plates, and were developed with 5% H_2SO_4 in methanol (plus heat). Analytical HPLC was performed with a system consisting of two 4 mm x 30 cm -porasil silica columns (Waters 27477) or two similar Hibar-II columns (Merck 906006-94) in series and the following Waters components: 6000 SDS pump, U6K injector, and 401 differential refractometers detector. Analysis were performed at 2 mL/min with mixtures of ethyl acetate and hexane as noted below. Flash chromatography was done by the Still procedure.

Dimethoxyethane and methylene chloride were distilled from CaH_2 and stored over 4A molecular sieves. N-bromosuccinimide (NBS) was recrystallized from chloroform, dried *in vacuo*, and stored cold. Pyridinium dichromate was prepared by the procedure of Corey[47] and was stored in a dessicator over Drierite. Sodium hydride was employed as a granular powder, Butyl lithium in hexane was purchased from Alfa Vention.

EXPERIMENTAL DATA

Isolation of Loganin 1

A total of 750 g of air dried chopped pulp of Strychnos nux Vomica and 1000 mL of chloroform/methanol (4:1) was refluxed at 75°C for 7.0 - 8.0 hr. The mixture was filtered and the extraction was repeated twice with fresh solvent. All extracts were combined and concentrated to a syrupy consistency. Crystallization was allowed to progress for 2 days, then the crystals were separated from the mother liquor and recrystalized three times from absolute ethanol, resulting in 8.5-10.5 g of pure loganin (1.1-1.4 % yield based on air dry fruit pulp weight), m.p. 220-223°C, mixed m.p. 221-224°C. TLC (Ethanol/Acetone:2/1), R_f = 0.78-0.79, IR ($CHCl_3$): 3600, 1722, 1660 cm^{-1}. ^{1}HNMR (D_2O): 7.20 (1H,s); 3.65 (3H,s); 1.05 (3H,d).

Acetylation of Loganin

To 0.5 g of loganin 1, dissolved in 5.0 mL of pyridine was added 4.0 mL of acetic anhydride. The mixture was refluxed for 1 to 2 hours, then poured into 20 mL of crushed ice. The mixture was kept overnight in a refrigerator, then the precipitate was filtered, dissolved in ethanol/water (3/1) mixture and recrystalized twice to give 630 mg (82%) of loganin pentaacetate, mp 139-140°C. TLC

(Hex/EtOAc:2/1) R_f = 0.62; (Chloroform/Ether:1/1) R_f = 0.45; ^{1}HNMR ($CDCl_3$): 7.10 (1H,s); 3.70 (3H,s); 2.0-2.20 (15H,d). IR ($CHCl_3$): 1765, 1645, 1070 cm^{-1}.

Hydrogenation of Loganin Pentaacetate 2

A mixture of 1.000 g (1.700 mmol) of loganin pentaac tate and 0.500 g (2.200 mmol) of PtO_2 in 100 mL of glacial acetic acid was hydrogenated at 1 atm. for 3 hour at room temperature. After filtration of the catalyst, concentration of the filtrate in vacuo gave 1.065 g of oily, yello wish crude product. The oily product was diluted with 20.0 mL of absolute ethanol, a little decolorizing carbon was added, and the mixture was filtered through a Celite pad. Concentration in vacuo gave 980 mg (98%) of a colorless oil showing one spot on TLC ($CHCl_3/Et_2O$:1/1). Crystallization from ethanol gave 868 mg (87%) of white needles of dihydro-loganin pentaacetate, m.p. 133-135°C. Anal. : Calcd. for $C_{27}H_{38}O_{15}$, C = 53.28 , H = 6.36 Found: C = 53.70 , H = 6.44. ^{1}HNMR (CD_3COCD_3); 5.50-4.10 (7H,m); 3.75 (3H,s); 3.10-2.10 (5H,m); 2.25-2.00 (20H,m); 1.00 (3H,d). IR (CCl_4): 1750, 1760 cm^{-1}. TLC ($CHCl_3/Et_2O$:1/1) R_f = 0.69-0.70 .

Hydrogenation of Loganin

A mixture of 250 mg (0.600 mmol) of loganin and 125 mg (0.550 mmol) of PtO_2 in 25.0 mL glacial acetic acid was

hydrogenated at 1 atm. for three hour at room temperature. Filtration of the catalyst and concentration of the filtrate gave 247 mg (99%) of oily clear substance. TLC (Et_2O/EtOH:4/1) showed only one spot and no vinyl hydrogens were apparent in the ^{1}HNMR (D_2O) spectrum. The product obtained was acetylated directly in the next step.

Acetylation of Dihydrologanin

To a mixture of 229 mg (0.580 mmol) of dihydrologanin and 20.0 mL of pyridine, 5.00 mL of acetic anhydride was added. The reaction mixture was refluxed at 110-112°C for 4 h, then cooled to room temperature and diluted with 200 mL of water, but no precipitate appeared. The mixture was extrac ted with CH_2Cl_2 (2x50 mL), wich was dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give 312 mg (89%) of oily brownish material. Addition of 20.0 mL CH_2Cl_2 and treatment with a little decolorizing carbon afforded a brown solid upon concentration. Crystallization from absolute ethanol gave 298 mg (85%) of white needles of dihydrologanin penta-acetate with m.p. 134-135°C, mixed m.p. 134-136°C. Comparison of ^{1}HNMR and IR spectra and TLC R_f's showed this sample of dihydrologaninpentaacetate to be idintical with that prepared above.

Glucose Cleavage From Loganin Using $BF_3.Et_2O$

A mixture of 150 mg (0.384 mmol) of loganin 1, 3.0 mL acetic anhydride and 0.80 mL of boron trifluoride etherate

was stirred at room temperature until TLC showed the reaction was complete (four days). The reaction mixture was neutralized by addition of 15-20 mL of saturated aqueous sodium bicarbonate, then extracted with ethyl acetate (4x50 mL). The combined organic extracts were dried over sodium sulfate (anhydrous), concentrated and dried *in vacuo*. The diacetate was isolated by flash chromatography with hexane/ethylacetate:2/1. Fractions of the desired product were combined, concentrated and dried *in vacuo* to give 90 mg (79%) of **6** as a light yellow oil, TLC (Hex/EtOAc:2/1) R_f = 0.58-0.59 . Anal. : Calcd. for $C_{15}H_{20}O_7$: C, 58.71; H, 6.41. Found: C, 58.21; H, 6.73. IR ($CHCl_3$): 1735, 1700, 1635 cm^{-1} ; ^{1}HNMR (CCl_4): 7.25 (1H,s); 6.20 (0.4H,d, J=4.0 Hz); 5.95 (0.6H,d, J=4.0 Hz); 5.10 (1H,br,m); 3.70 (3H,s); 2.25 (3H,s); 2.10 (3H,s); 1.10-3.20 (5H,m); 1.05 (3H,br,d).

Hydrolysis of Loganin 1,6 Diacetate to Hemiacetal 7

A mixture of 50 mg (0.162 mmol) of diacetate **6**, and 3.0 mL of tetrahydrofuran:glacial acetic acid:con.hydrochloric acid (1:1:1) were stirred at 2-5°C. After seven hours TLC showed the reaction was complete. The reaction was diluted with 10-15 mL of saturated aqueous sodium bicarbonate, then extracted with ethyl acetate (3x50 mL). The combined organic extracts were dried *in vacuo*, and the hemiacetal was isolated by flash chromatography

(Hex/EtOAc:2/1) to give 34 mg (88%) of 7 as a yellow oil, TLC (Hex/EtOAc:2/1) R_f = 0.40-0.41 . Anal. : Calcd. for $C_{13}H_{18}O_6$: C, 57.79; H, 6.67. Found: C, 57.64; H, 6.81. ^{1}HNMR (CCl_4): 7.20 (1H,br,s); 3.75 (3H,br,s); 2.15 (3H,s); 1.20-5.40 (8H,m); 1.10 (3H,m). IR ($CHCl_3$): 3605, 1740, 1640 cm^{-1}.

Wadsworth Emmons Reaction of Hemiacetal Monoacetate 7

A suspension of 15 mg (0.630 mmol) of sodium hydride granules in 2.0 mL of dry DME (CaH_2) was prepared under a positive pressure of dry nitrogen. A solution of 70 mg (0.315 mmol) of dimethyl-2-oxoheptyl phosphonate in 1.0 mL of dry DME was added to this stirred suspension, and stirring was continued at room temperature for 15 min. (a white ppt. formed). This mixture was cooled in an ice bath, and a solution of 85 mg (0.315 mmol) of hemiacetal monoacetate 7 in 1.0 mL of dry DME was added all at once. Stirring was continued, with ice cooling, for an additional 30 min. followed by another 30 min. at room temperature. After a total of two hours, the reaction was complete (TLC, Hex/EtOAc:3/1). The reaction was quenched by adding 2.0 mL of glacial acetic acid, then poured into 50 mL of water and extracted with ethyl acetate (3x50 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated on the roto-vap to give 98 mg of crude yellow gum. This was chromatographed using preparative thin layer chromatography (Hex/EtOAc:2/1) to give 87 mg (76%) of

8 as a very light yellow oil, TLC (Hex/EtOAc:2/1) R_f = 0.37-0.38. Anal. : Calcd. for $C_{20}H_{30}O_6$: C, 65.59; H, 8.20. Found: C, 65.30; H, 8.39. IR ($CHCl_3$): 1735, 1725, 1650 cm^{-1}; ^{1}HNMR ($CDCl_3$): 7.50 (1H,s); 5.20 (1H,m); 4.10 (1H,d,d,d); 3.70 (3H,s); 3.00 (1H,br,m); 2.05 (3H,s); 1.60-2.80 (12H,m); 1.15 (2H,br,m); 1.05 (3H,d); 0.90 (3H,t).

Preparation of Bromo-Lactone 10

To a solution of 150 mg (0.250 mmol) of loganin pentaacetate 2 in 5.0 mL of dry CH_2Cl_2 (CaH_2) under nitrogen was added 90 mg (0.506 mmol) of NBS, the mixture was stirred for 3 min, then 100 mg (0.265 mmol) of PDC was added to the reaction mixture. The reaction was followed by TLC and was complete after 24 hours. The reaction mixture was diluted with 50 mL of ether, then filtered and evaporated to give a residue of 168 mg. Upon flash chromatography (Hex/EtOAc;1/1) this gave 145 mg (88%) of a yellowish white solid, m.p. 174-176°C, TLC (Hex/EtOAc:1/1) R_f = 0.51-0.52 . Anal. : Calcd. for $C_{27}H_{35}O_{16}Br$: C, 46.65; H, 5.04 ; Br, 11.49. Found: C, 46.52; H, 5.15; Br, 11.67 . IR ($CHCl_3$): 1765, 1740, 1220 cm^{-1}. ^{1}HNMR (CCl_4): 5.90 (1H,br,d); 4.95-5.30 (6H,m); 4.2 (3H,br,s); 3.80 (3H,s); 1.95-2.15 (15H,m); 1.10 (3H,br,d). MS (m/e): 367, 369, 317, 319.

Preparation of Lactone 11 from Bromo-Lactone 10

To a stirred solution of 80 mg (0.115 mmol) of Bromo-lactone 10 in 6.0 mL of dry CH_2Cl_2 at room temperature was added a premixed solution of 13 mg (0.198 mmol) of Zn powder and 0.3 mL of glacial acetic acid. After 60 min. the reaction mixture was diluted with 25 mL of CH_2Cl_2, filtered, washed twice with 5% sodium bicarbonate and finally with water. The organic layer was dried over sodium sulfate and concentrated in vacuo to yield 76 mg of crude lactone. Upon purification by flash chromatography (Hex/EtOAc:3/2) this gave 68 mg (96%) of a white solid , m.p. 167-168°C . TLC (Hex/EtOAc:1/1) R_f = 0.40-0.41 . Anal. : Calcd. for $C_{27}H_{38}O_{16}$: C, 52.62; H, 5.90 . Found: C, 52.56; H, 6.12 . IR ($CHCl_3$): 1735, 1765, 1230 cm^{-1}. ^{1}HNMR ($CDCl_3$): 4.95-5.60 (5H,m); 4.20 (3H,br,m); 3.75 (3H,s); 3.20 (2H,br,m); 2.10 (20H,m); 1.15 (3H,d). MS (m/e): 331, 269, 209, 109.

Preparation of Gem-dimethyl Enone 23

A suspension of 4.00 mg (0.167 mmole) granular NaH in 2.00 mL of dry DME (CaH_2) was prepared under nitrogen and a solution of dimethyl (2-oxo-3,3-dimethyl-heptyl)-phosphonate 22 (45.0 mg, 0.180 mmole) in 1.00 mL of dry DME was added to this stirred suspension. Stirring was continued for 30 min. at room temperature, the mixture was then cooled to -78°C

and a solution of 40.0 mg (0.165 mmole) of aldehyde 13 in 1.00 mL dry DME was added all at once. This mixture was stirred 1 h. at -78°C, then for 4 h. at room temperature, until reaction was complete (TLC, Hex/EtOAc:3/1). The reaction mixture was neutralized with acetic acid, diluted with 10 mL of water and extracted with ethyl acetate (3x50 mL). The organic layer was washed with water, dried over anhydrous Na_2SO_4, then concentrated in vacuo to obtain 61.0 mg of the crude product. TLC (Hex/EtOAc:3/1) showed a UV active spot at R_f = 0.47 which proved to be the desired product. Separation of the product on the Chromatotron (Hex/EtOAc:5/1) gave 49.0 mg (81%) of a thick, clear liquid. ^{1}HNMR (200 MHz) and HPLC (Hex/EtOAc:4/1) showed the material to be a 8:1 mixture of epimers. Anal. : Calcd. for $C_{21}H_{34}O_5$: C, 68.86; H, 9.29. Found: C, 68.72; H, 9.52. IR ($CHCl_3$): 1615, 1685, 1720 cm^{-1} ; ^{1}HNMR (400MHz; Prostaglandin numbering):

Cis Isomer, 23B:

6.69 (d,d 1H, $J_{13,14}$ = 15.0 Hz, $J_{13,12}$ = 10.0 Hz, H-13), 6.45 (d, 1H, $J_{14,13}$ = 15.2 Hz, H-14), 5.22 (m, 1H, H-10), 3.60 (s, 3H, OMe), 2.83 (d,d,d,d,d, 1H, J_{avg} = 8.3 Hz, H-8), 2.62 (d,d,d, 1H, J_{avg} = 9.8 Hz, H-12), 2.34, 2.17 (d,ABq, 2H, $J_{7A,7B}$ = 15.7 Hz, $J_{7A,8}$=6.8 Hz, $J_{7B,8}$ = 9.0 Hz, H-7A,7B), 2.03 (s, 3H, CH_3CO), 1.96-2.08 (m, 2H, H-9A,11), 1.69 (d,d,d, 1H, $J_{9B,8}$ = 8.6 Hz, $J_{9B,9A}$ = 14.1 Hz, $J_{9B,10}$ = 5.1 Hz, H-9B), 1.49, 1.49 (t, 2H, $J_{17A,18}$ = 9.5 Hz; t, 1H,

$J_{17B,18}$ = 7.3 Hz, H-17A,17B), 1.24 (t,q, 2H, $J_{19,18}$ = 7.0 Hz, $J_{19,20}$ = 7.0Hz, H-19), 1.089 (s, 3H, H-21), 1.085 (s, 3H, H-22), 1.17-1.03, (m, 2H, H-18), 0.86 (d, 3H, $J_{23,11}$ = 6.7 Hz, H-23), 0.84 (t, 3H, $J_{20,19}$ = 7.0Hz, H-20).

Trans Isomer, 23 A:

6.82 (d,d, 1H, $J_{13,14}$ = 15.0 Hz, $J_{13,12}$ = 8.8 Hz, H-13), 6.40 (d, 1H, $J_{14,13}$ = 15.2 Hz, H-14), 5.17 m, 1H, C-10), 3.61 (s, 3H, OMe), 2.43 (m, 3H, H-8,11,12), 2.36, 2.24 (d,ABq, 2H, $J_{7A,7B}$ = 15.0 Hz, $J_{7A,8}$ = 5.3 Hz, $J_{7B,8}$ = 8.2 Hz, H-7A,7B), 2.11-2.03 (m, 1H, H-9A), 2.04 (s, 3H, CH_3CO), 1.67 (d,d,d, 1H, $J_{9B,8}$ = 8.2 Hz, $J_{9B,9A}$ = 14.5 Hz, $J_{9B,10}$ = 6.3 Hz, H-9B), 1.493 (t, 1H, $J_{17A,18}$ = 7.4 Hz, H-17A), 1.493 (t, 1H, $J_{17B,18}$ = 9.4 Hz, H-17B), 1.24 (t,q, 2H, $J_{19,18}$ = 7.4 Hz, $J_{19,20}$ = 7.0 Hz, H-19), 1.15-1.05 (m, 2H, H-18), 1.092, s, 3H, H-21), 1.085 (s, 3H, H-22), 0.84 (t, 3H, $J_{20,19}$ = 7.2Hz, H-20), 0.81 (d, 3H, $J_{23,11}$ = 6.3 Hz, H-23).

Preparation of Phosphonate Reagent 22

To a cold (-78°C) solution of 170 mg (1.37 mmole) of dimethyl methylphosphonate in 15.0 mL of dry DME (CaH_2) was added dropwise, with stirring during 15 min, 1.60 mL of a hexane solution containing 2.73 mmol of n-BuLi. After the resulting cold suspension had been stirred for 30 min, a solution of 215 mg (1.36 mmole) of gem-dimethyl ester 21 in 1.00 mL dry DME was added dropwise and with stirring during

30 min. The resulting cold (-78°C) mixture was stirred for an additional 30 min, and then the cooling bath was removed and stirring was continued for 3 h. The resulting mixture was diluted with 15 mL of water, then extracted with chloroform (3x20 mL). The aqueous layer was acidified with 1N HCl and again extracted with chloroform (3x20 mL). The combined organic layers were washed with saturated NaCl, dried and concentrated to leave 355 mg of the crude product as a pale yellow liquid. NMR showed the formation of the desired phosphonate. Also, TLC (Hex/EtOAc:1/1) showed a blue spot at R_f = 0.67 upon spraying with phosphonate reagent. Bulb to bulb distillation gave 260 mg (76% yield) of the phosphonate 22, bp 114-122°C/0.25 mm. ^{1}HNMR ($CDCl_3$): 3.80 (6H,d, J=12.0 Hz); 3.20 (2H,d, J=22 Hz); 0.85-1.20 (15H). IR ($CHCl_3$): 1710, 1305 cm^{-1}.

Preparation of Gem-dimethyl Ester 21 Using Diazomethane

To a stirred solution of 500 mg (3.47 mmole) of 2,2-dimethyl hexanoic acid 20 in 5.0 mL of dry ether at 15-20°C was added dropwise 5.0 mL of a solution of diazomethane in ether (Org. Syn. Coll. Vol 2. p 461). Stirring was continued at 15-20°C until nitrogen evolution ceased and the mixture became slightly yellow. The reaction mixture was stirred for an additional 30 min, then concentrated *in vacuo* to give 484 mg of methyl 2,2-dimethyl hexanoate 21. NMR and IR showed the formation of the desired ester in 88% yield

after distillation (178-184°C/760 mm). ^{1}HNMR (CDCl3): 3.65 (3H,s); 0.70-1.70 (15H). IR ($CHCl_3$): 1735 cm^{-1}.

Preparation of Gem-dimethyl Acid 20 Using Cu_2O (catalyst)

Sulfuric acid (96%, 270 mL , 497 g , 4.9 moles) was poured into a 500 mL three-necked flask fitted with a magnetic stirrer, pressure equalizing dropping funnel, and a thermometer that dipped into the acid. The reaction mixture was stirred slowly and maintained at 15-20°C by means of a cooling bath as 5-8 drops of 85% formic acid were added. Under the same conditions 0.36 g (0.003 mole) of Cu_2O was added, followed by a solution of 28.5 g (0.25 mole) of 2-methyl-2-hexanol 19 in 46.0 g (1.00 mole) of 85% formic acid added dropwise in the course of 45 minutes. The reaction mixture foamed during the addition, became a creamy color, and was stirred for additional 30 minutes at 15-20°C after the addition was complete. The reaction mixture was then poured with stirring onto 500 g of crushed ice in 2.0 L beaker, and extracted with ether (3x200 mL). The combined ether solutions were extracted with saturated $NaHCO_3$ (2x100 mL). The aqueous solution was back extracted with (2x100 mL) of ether to remove traces of neutral material, then acidified to pH 2.0 with 12N HCl. The carboxylic acid was taken up in 200 mL of ether, and the aqueous layer was extracted with 200 mL of ether, and the combined ether layers were washed with 75 mL of water, then dried over

anhydrous Na_2SO_4 and concentrated *in vacuo* to give, after distillation at 232-238°C/760 mm., 25.1 g (70 %) of 2,2-dimethyl hexanoic acid 20. ^{1}HNMR ($CDCl_3$): 12.20 (1H,br,s). IR ($CHCl_3$): 1695 cm^{-1}.

Preparation of Gem-dimethyl Ester 21 Using HCl-MeOH

Under a positive pressure of dry nitrogen, 0.7-0.9 mL of acetyl chloride was added dropwise to 25 mL of dry MeOH. To this stirred solution, at room temperature, was added 4.00 g (0.028 mole) of 2,2- dimethyl hexanoic acid 20, followed by 3.40 mL (3.04 g, 0.029 mole) of methyl orthoformate. The solution was stirred overnight at rt. and then concentrated *in vacuo*. The residue was distilled at 177-182°C/760 mm to gave 3.45 g of methyl 2,2-dimethyl hexanoate 21 (79% yield). ^{1}HNMR ($CDCl_3$): 3.70 (3H,s); 0.70-1.75 (15H). IR ($CHCl_3$): 1740 cm^{-1}.

Preparation of Tertiary Alcohol 19

The alcohol was prepared by Grignard reaction using 4.53 g (0.186 mole) of magnesium turnings, 25.5 g (0.186 mole) of n-butyl bromide, and 13.7 mL (10.83 g, 0.186 mole) of dry acetone, and gave 17.35 g (80%) of 2-methyl-2-hexanol (bp 140-143°C). ^{1}HNMR and IR were identical with Aldrich catalogue entries for this compound. ^{1}HNMR ($CDCl_3$): 2.95 (1H,s,br); 0.75-1.25 (15H). IR ($CHCl_3$): 3590 cm^{-1}.

Preparation of Methyl 2,2 Dimethylhexanoate

A dry 200 ml round bottom flask equiped with a magnetic stirrer was flushed with dry nitrogen. Butyl lithium (1.6 M in hexane, 20.0 ml, 0.032 mol) was introduced and the flask was immersed in dry-ice bath at -78°C. Diisopropyl-amine (4.5 ml, 3.24 g, 0.032 mol) was added and the mixture was stirred for 30 minutes at -78°C, then diluted with 10 ml of dry THF. Methyl isobutyrate (3.26 g, 0.032 mol) was added dropwise over a period of 5 minutes, followed after 15 minutes by butyl iodide (5.89 g, 0.032 mol) also added dropwise over period of 5 minutes. Stirring was continued for 30 minutes at -78°C, then, slowly, the reaction temperature raised to room temperature while stirring was conti nued for an additional 30 minutes. The reaction was then quenched with 15 ml of 20% hydrochloric acid. The organic layer was separated, and the aqueous layer was extracted with two 25 ml portions of ether. The combined organic extracts were washed with two 10 ml portions of saturated aqueous sodium bicarbonate and dried over anhydrous Na_2SO_4. Distillation produced 4.52 g (89%) of pure methyl 2,2 dimethylhexanoate, bp 179-182°C/760 mm, identical to the compound 21 prepared by the formic/sulfuric acid route above. ^{1}HNMR ($CDCl_3$): 3.75 (3H, s); 0.70-1.80 (15H). IR ($CHCl_3$): 1745 cm^{-1}.

Preparation of Enone 9

A solution of 0.210 g (0.880 mmol) of dimethyl 2-oxoheptylphosphonate in 1.00 mL of dry DME was injected into a stirred suspension of 0.021 g of granular NaH (0.874 mmole) in 5.00 mL of dry DME (CaH_2) under a blanket of dry nitrogen. The stirring was continued at rt. for one hour, while a voluminous white ppt. formed. The reaction mixture was cooled in an ice bath and a solution of 0.210 g (0.869 mmole) of aldehyde 13 in 2.00 mL of dry DME was injected all at once into the reaction mixture. Stirring was continued with ice cooling for 30 min. followed by three hours at rt. The reaction mixture was neutralized with acetic acid and extracted with ethyl acetate (3x50 mL). The combined organic layers were dried and concentrated in vacuo to give 230 mg of crude product. Purification on the Chromatotron (Hex/EtOAc:3/1) gave 200 mg (89%) of the desired Wittig adduct 9, as a 9/1 mixture of C-12 epimers with a UV active spot at R_f = 0.42-0.44 (same solvent system). IR ($CHCl_3$): 1725, 1695, 1620 cm^{-1}. ^{1}HNMR ($CDCl_3$): 6.80 (1H,d,d, J=7.5 Hz, 15.0 Hz); 6.05 (1H,d, J=15.0 Hz); 5.20 (1H,br,m); 3.65 (3H,s); 2.15 (3H,s); 1.15-2.80 (18H,m); 0.80 (3H,m). Anal. : Calcd. for $C_{19}H_{30}O_5$: C, 67.47 , H, 8.88. Found: C, 67.39 ; H, 8.64 .

Preparation of Aldehyde 13

A solution of 1.00 g (1.62 mmole) of loganin

pentaacetate lactone 11 in 100 mL of 5:1 AcOH/H_2O was maintained at 120-125°C for 36 h. The reaction mixture was then cooled and concentrated on the rotovap and the residue was further dried in vacuo to give 880 mg of crude product showing both aldehydic and carboxylic protons in the ^{1}HNMR. The crude product was diluted with 10.0 mL of water, acidified with 0.1N HCl, then extracted with ethyl acetate (3x50 mL). The combined organic layers were separated, washed with water and dried over anhydrous Na_2SO_4 to give 285 mg of crude product 12 which again proved to be a mixture of the acid and the aldehyde. A Benedict's test on the aqueous layer, indicated that glucose was present.

To the crude aldehyde/acid mixture without further purification, 5.00 mL of ether was added, followed by excess ethereal diazomethane with stirring at rt. Stirring was continued for an additional 30 min., then the mixture was concentrated in vacuo to give 280 mg of residue. After purification on the Chromatotron (Hex/EtOAc:3/1) this gave 270 mg (69%) of ester-aldehyde 13 as a 2/1 mixture of C-12 isomers. Anal. : Calcd. for $C_{12}H_{18}O_5$: C, 59.52; H, 7.44 . Found: C, 59.67; H, 7.53 . ^{1}HNMR ($CDCl_3$): 9.65 (1H,d, J=4.0 Hz); 5.20 (1H,br,m); 3.65 (3H,s); 2.10 (3H,s); 1.15-3.35 (7H,m); 0.95 (3H,d). IR ($CHCl_3$): 1715, 1730 cm^{-1}, TLC (Hex/EtOAc:1/1) R_f = 0.65-0.67 .

Preparation of Lactone 11 (Using I_2/ZnI_2)

A solution of 600 mg (1.00 mmol) of loganin penta-

acetate 2 in 12 mL of dry methylene chloride was prepared in a 250 mL round bottom flask equipped with a magnetic stirrer and a reflux condenser under a nitrogen atmosphere. To this 500 mg of dry powdered molecular sieve 4A was added and then 760 mg of iodine (3.00 mmol) followed by a catalytic amount of ZnI_2 (5-10 mg). After 5 min. stirring at room temperature, 2.63 g (7.00 mmol) of pyridinium dichromate was added, and the reaction was refluxed in an oil bath at 57-60°C. After 18 hours at reflux the reaction mixture was cooled and poured into 50 mL of ethyl acetate, then filtered through a little anhydrous magnesium sulfate. The filter cake was rinsed with an additional 50 mL of ethyl acetate. The combined organic filtrates were concentrated in vacuo and the residue was flash chromatographed with (Hex/EtOAc:3/2) to give 480 mg (60%) of iodolactone 14.

This iodolactone was directly washed with (2 x 50 mL) 15% aqueous sodium thiosulfate. The combined aqueous layers were extracted with ethyl acetate (3 x 50 mL) and the combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo. Recrystallization of the residue from chloroform/ether mixture afforded 335 mg (90%) of loganin pentaacetate lactone 11, m.p. 166-168°C, identical to that previously prepared using NBS; mixed m.p. 165-168°C. TLC (Hex/EtOAc:1/1) R_f = 0.41-0.43 . ^{1}HNMR ($CDCl_3$): 4.85-5.70 (5H,m); 4.25 (3H,br,m); 3.85 (3H,s); 3.25 (2H,br,m); 2.10- 2.20 (20H,m); 1.10 (3H,d). IR ($CHCl_3$): 1735, 1740, 1760, 1225 cm-1.

Decarboxylation of Lactone 11

To a stirred mixture of 100 mg (0.162 mmol) of lactone 11 in 2.0 mL of HMPA, 164 mg (0.81 mmol) of hydrated $MgCl_2$ was added. The reaction temperature was raised to 145-50°C and stirring was continued at this temperature. After one hour the reaction was complete and the reaction mixture was cooled to rt. and neutralized with ice cold 0.1N HCl. This mixture was extracted with ethyl-acetate (3 x 50 mL), and the combined organic layers were washed several times with water and dried over anhydrous Na_2SO_4. The ethyl acetate layer was concentrated to give 84 mg of crude product, which after purification on the Chromatotron (Hex/EtOAc:3/1), afforded 64 mg (69%) of lactone 15 as a white solid with m.p. 137-140°C. TLC (Hex:EtOAc/3:1) showed one spot at R_f = 0.52-0.53 . Anal. : Calcd. for $C_{25}H_{34}O_{14}$: C, 53.76; H, 6.14 . Found: C, 53.58; H, 6.08 . ^{1}HNMR ($CDCl_3$): 1.15 (3H,d); 2.15-2.25 (15H,m); 5.30 (1H,br,s). IR ($CHCl_3$): 1735, 1755 cm^{-1}.

Preparation of Malonic Ester-Aldehyde 16:(Methanolysis of 11)

A solution of 200 mg (0.325 mmol) of lactone 11 in 10.0 mL of dry MeOH was stirred at rt. under dry nitrogen. To this solution 44 mg (0.330 mmol) of dry K_2CO_3 was added. Reaction was complete after 2 min. at room temperature. The reaction mixture was neutralized with 0.1N HCl and extracted with methylene chloride (4 x 25 mL).

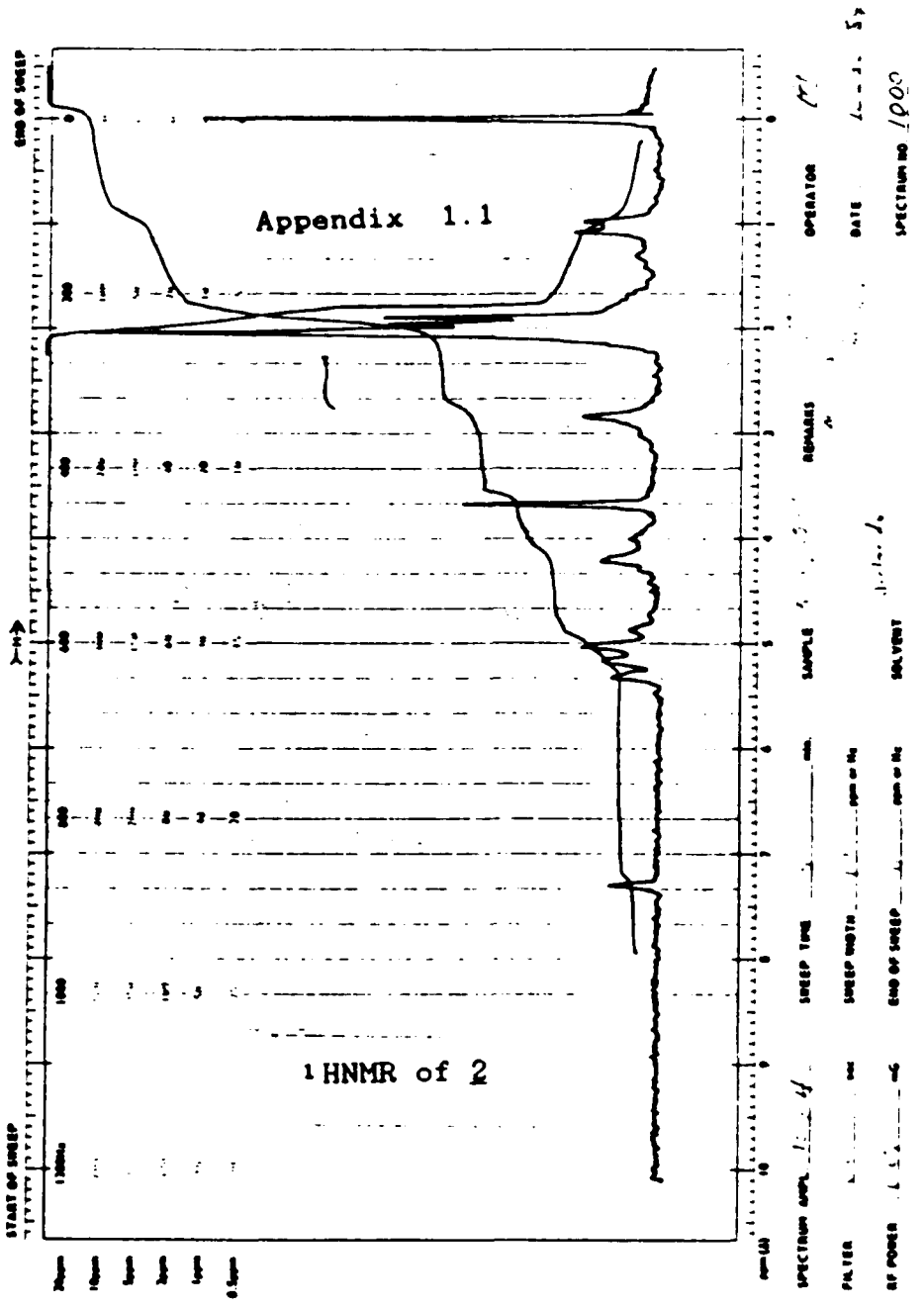
The combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by flash chromatography (Hex/EtOAc:1/1) to give 87 mg (89%) of **16**. IR ($CHCl_3$): 1750, 1740, 1645 cm^{-1}. ^1HNMR ($CDCl_3$): 1.10 (3H,d); 2.05 (3H,s); 3.65 (3H,s); 3.70 (3H,s); 9.70 (1H,d).

Methanolysis of Lactone 15

A solution of 30 mg (0.054 mmol) of lactone **15** in 5 mL of dry methanol was placed in a 50 mL round bottom flask fitted with a magnetic stirrer under a positive nitrogen pressure. To this mixture was added 31 mg (0.225 mmol) of anhydrous K_2CO_3. The reaction mixture was stirred at room temperature for three hours, cooled and neutrallized with 0.1 N HCl, then concentrated *in vacuo*. The residue was extracted with ether (3 x 20 mL), and the combined organic layers were dried *in vacuo* to give 14 mg of crude product **13**. TLC (Hex/EtOAc:1/1) R_f = 0.65-0.70 . ^1HNMR ($CDCl_3$): 1.00 (3H,d); 2.10 (3H,s); 3.60 (3H,s); 5.15 (1H,m); 9.60 (1H,d). IR ($CHCl_3$): 1730, 1720 cm^{-1}

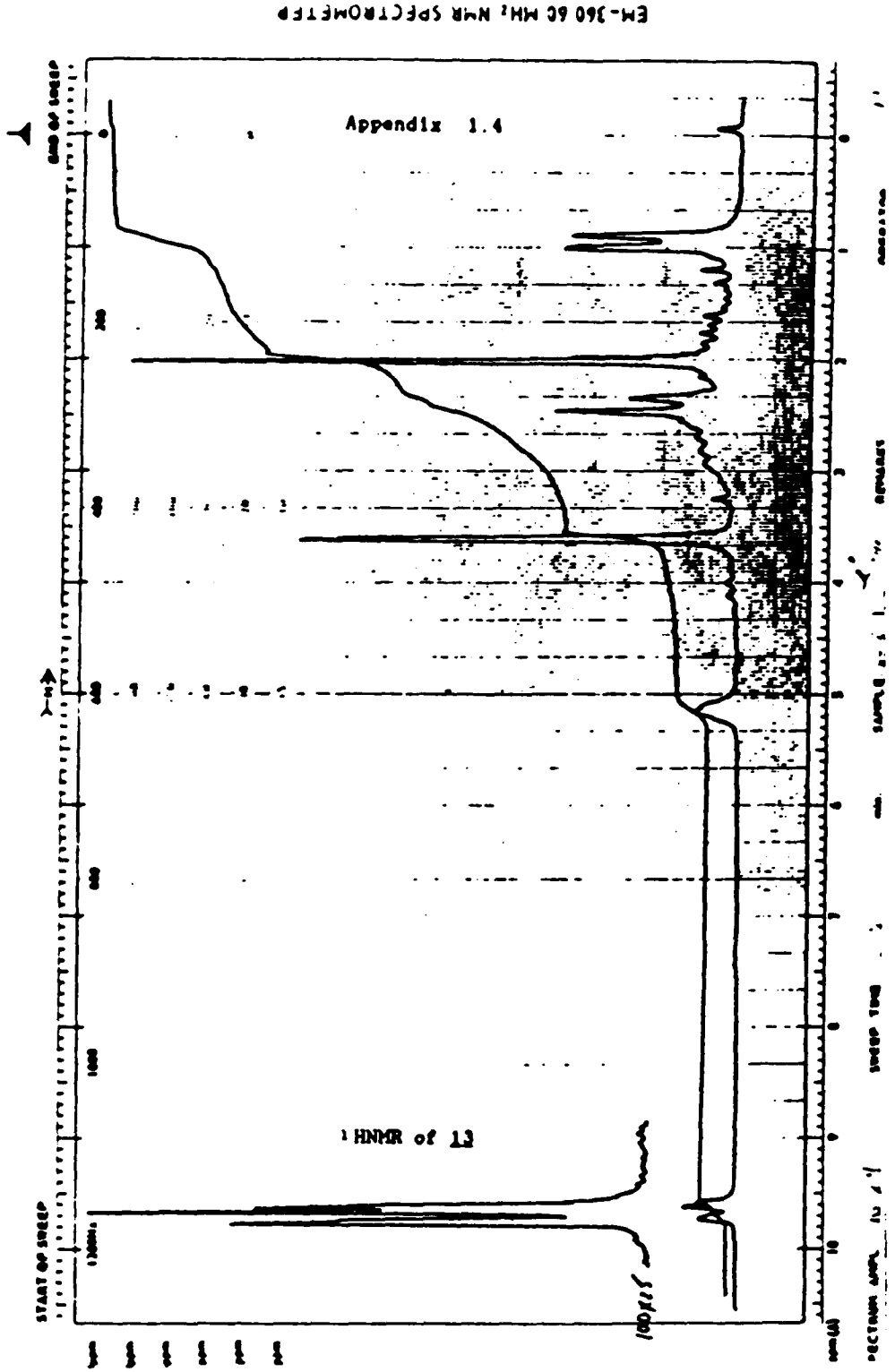
APPENDIX 1

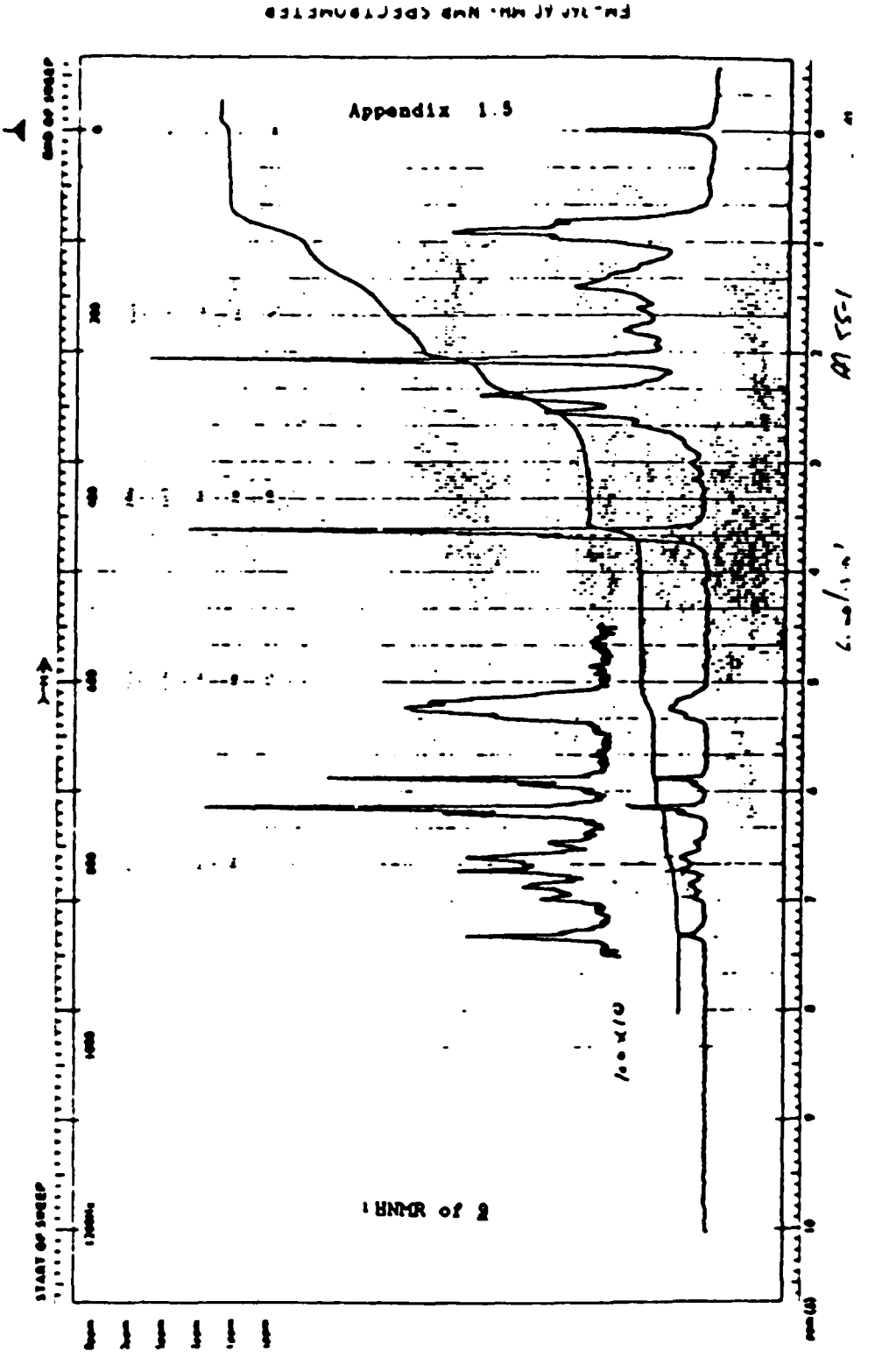
^{1}HNMR SPECTRA


EM-360 60 MHz NMR SPECTROMETER
Appendix 1.1
1HNMR of 2

EM-360 60 MHz NMR SPECTROMETER

EM-360 60 MHz NMR SPECTROMETER


EM-360 60 MHz NMR SPECTROMETER
Appendix 1.4
^{1}HNMR of 13

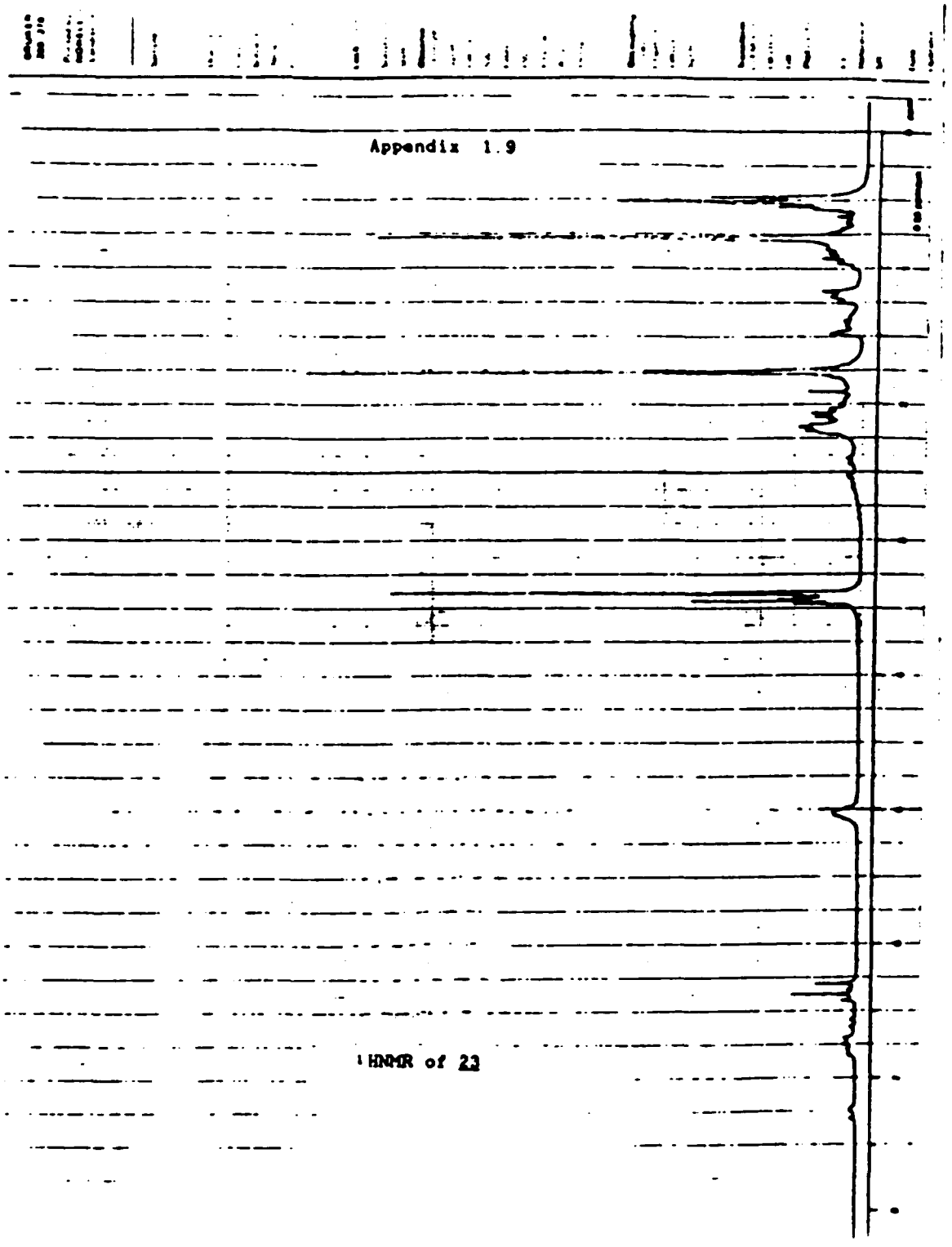

Appendix 1.5
1HNMR of 2

START OF SWEEP
END OF SWEEP
1HNMR of 8
100X
Appendix 1.8

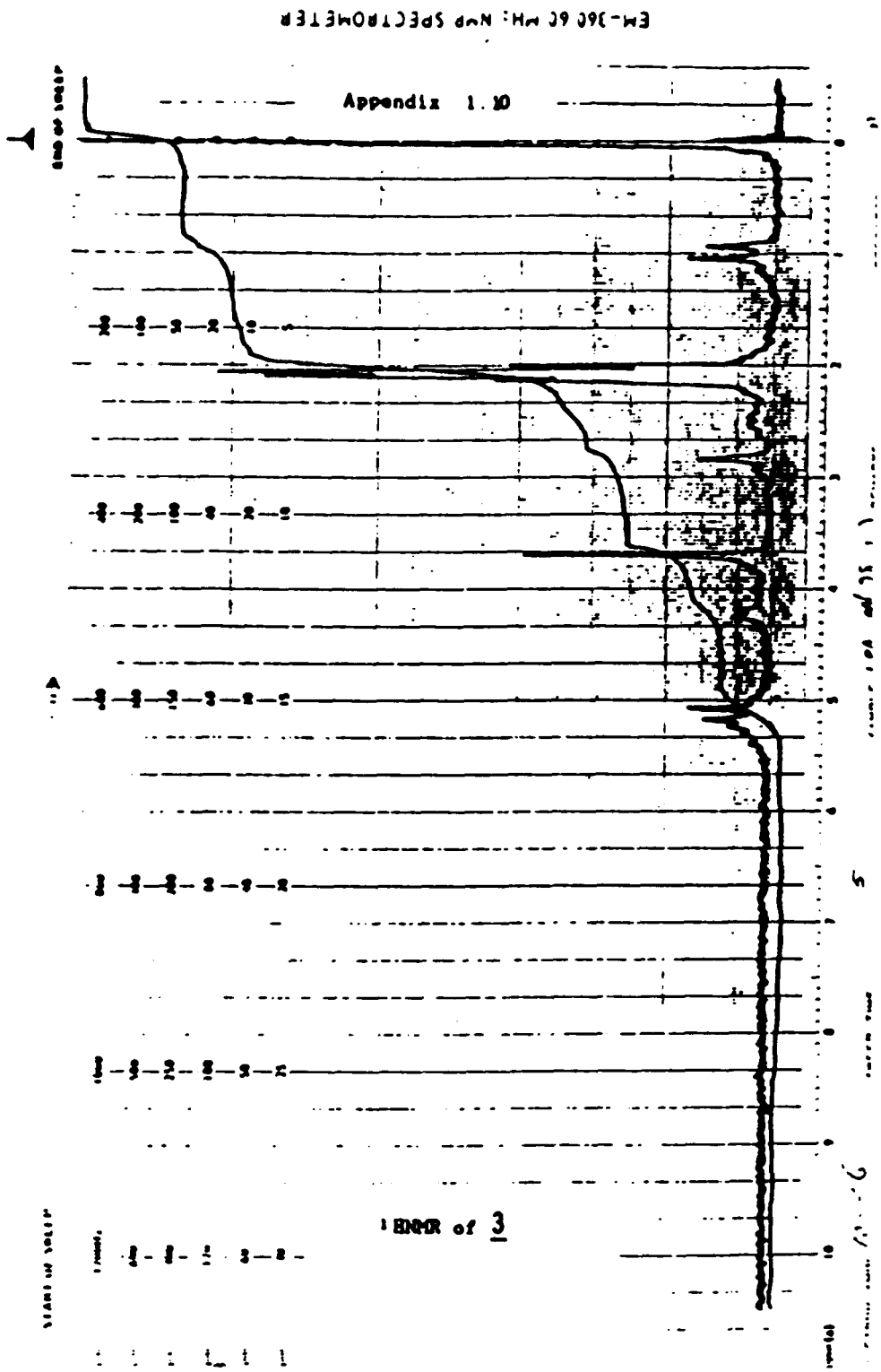
EM-360 60 MHz NMR SPECTROMETER

EM-360 60 MHz NMR SPECTROMETER

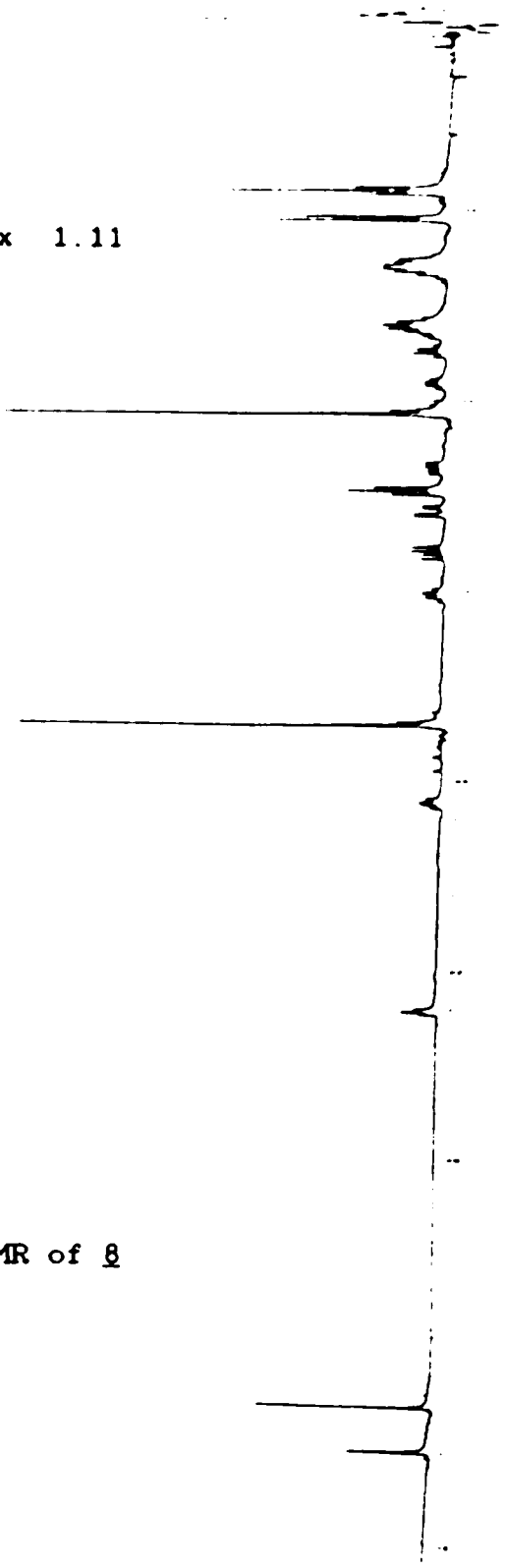
Appendix 1.9



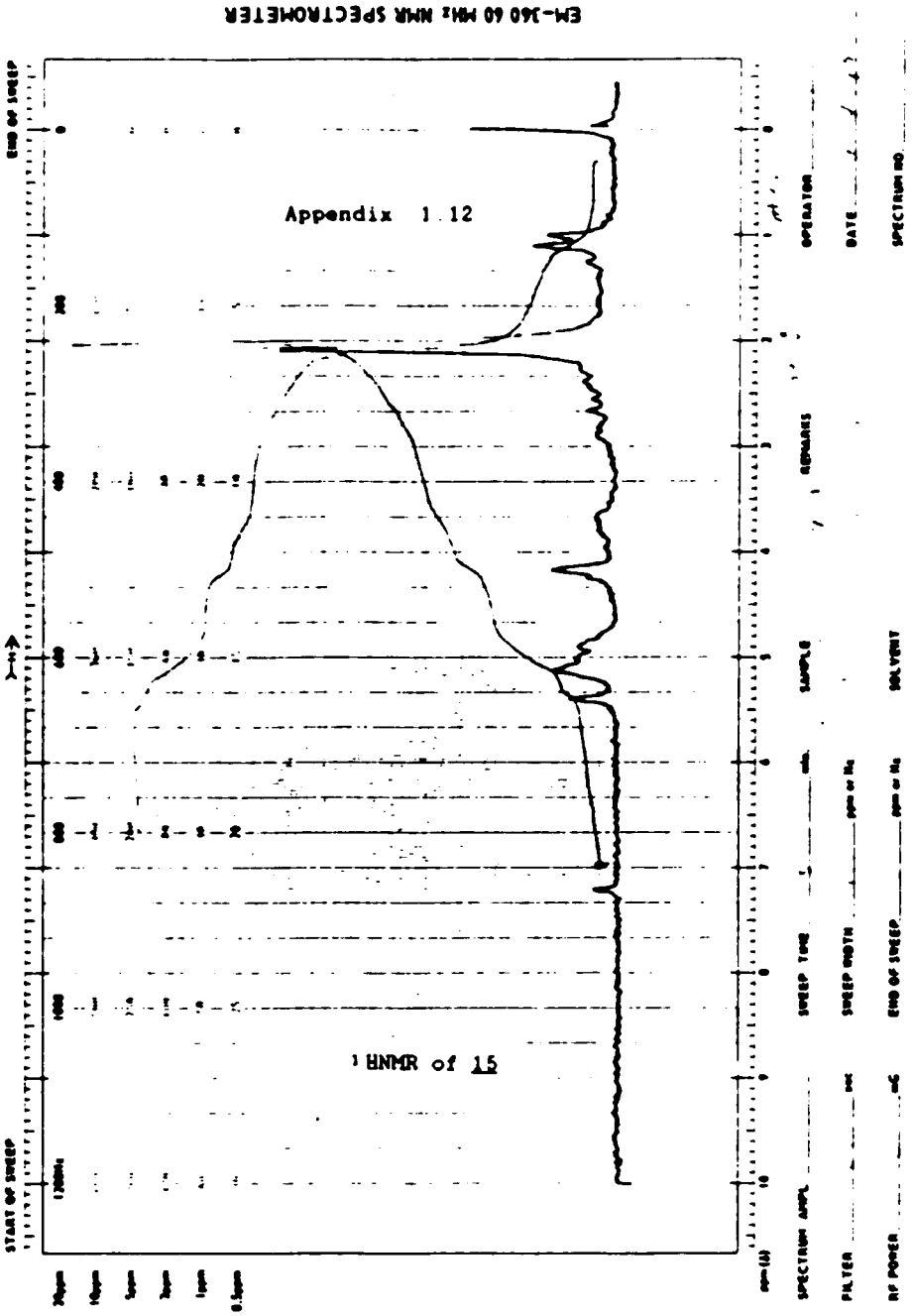
^{1}HNMR of 23

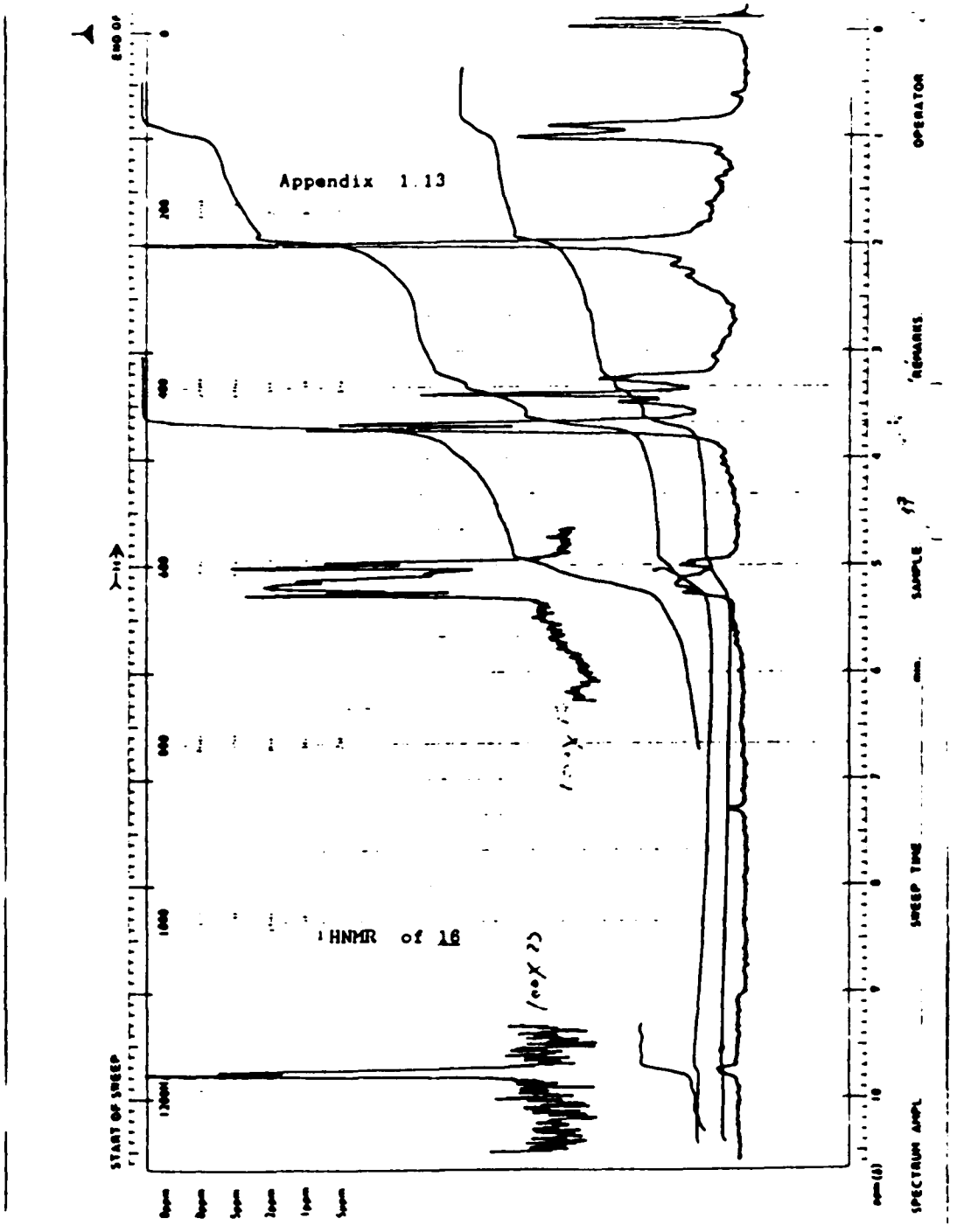

Appendix 1.10
ERROR of 3

Appendix 1.11



^{1}HNMR of 8

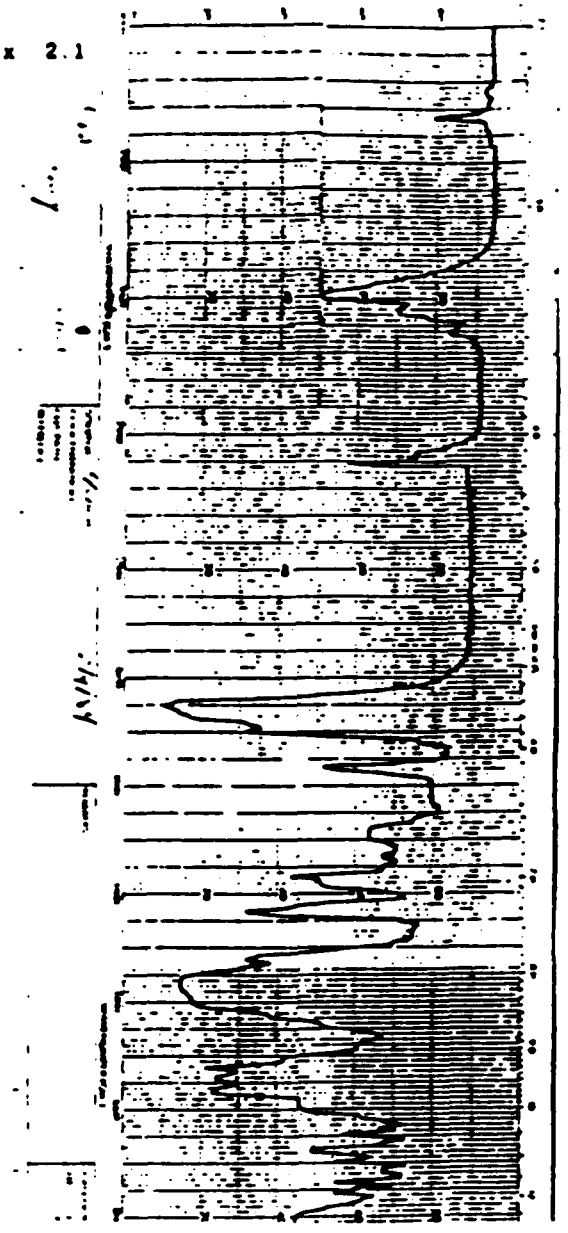

EM-360 60 MHz NMR SPECTROMETER
Appendix 1.12
^{1}HNMR of 15


Appendix 1.13
¹HNMR of 16

APPENDIX 2

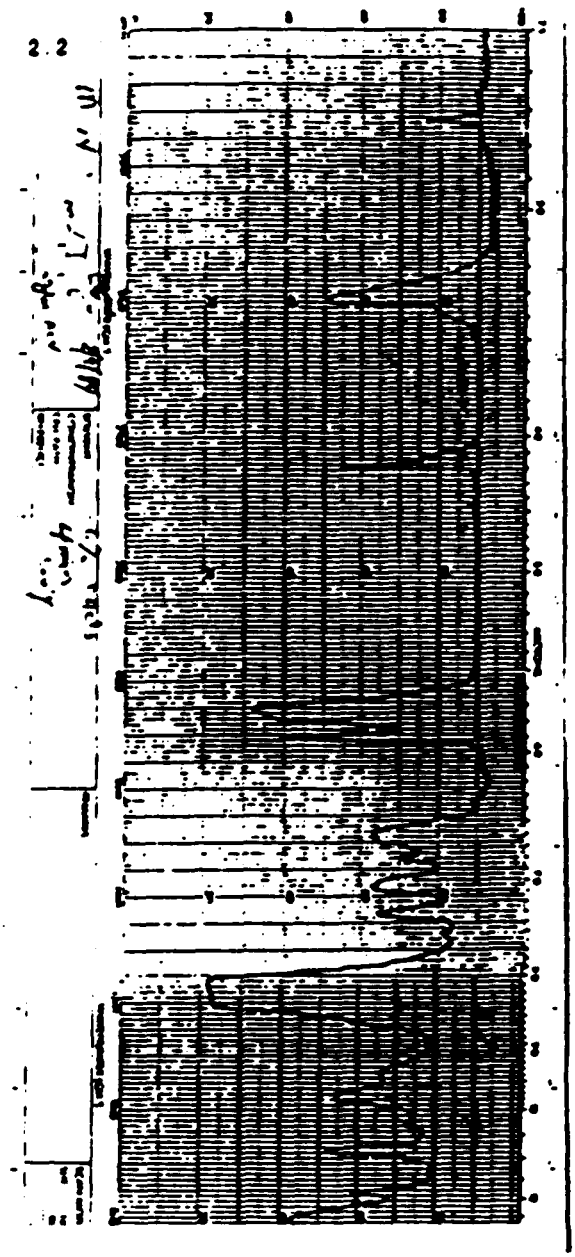
IR SPECTRA

Appendix 2.1



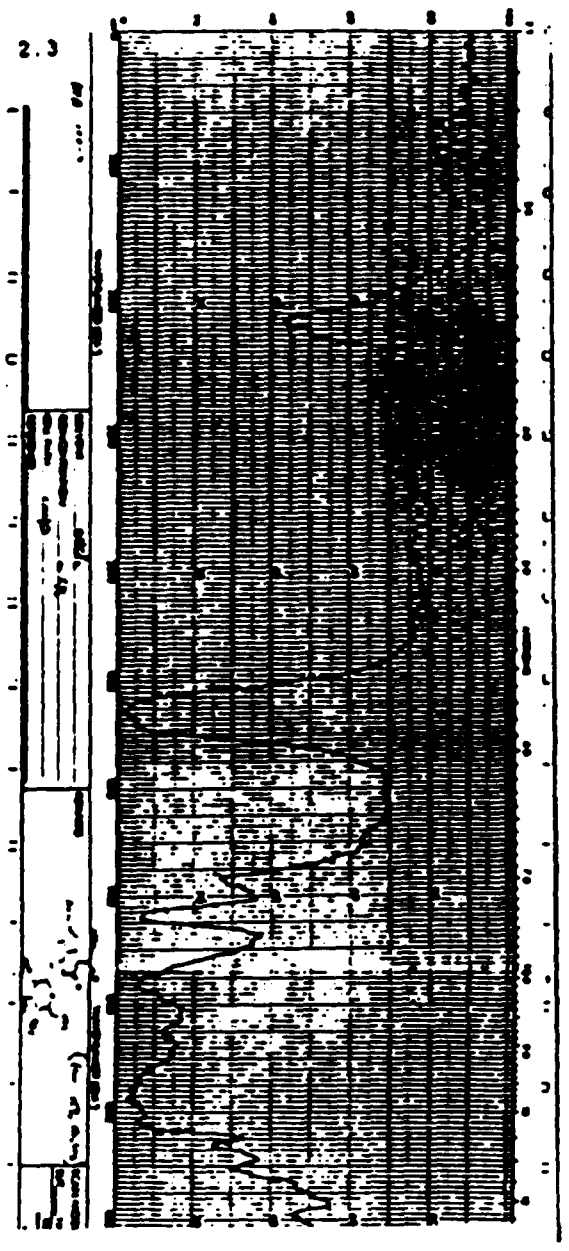
IR of 2

Appendix 2.2



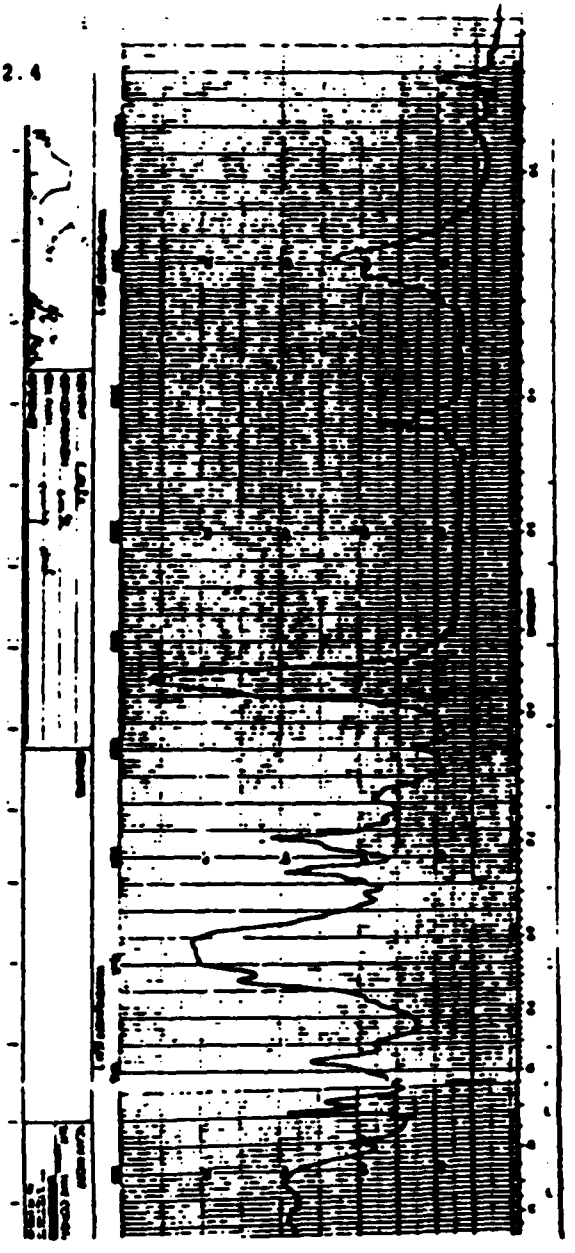
IR of 10

Appendix 2.3



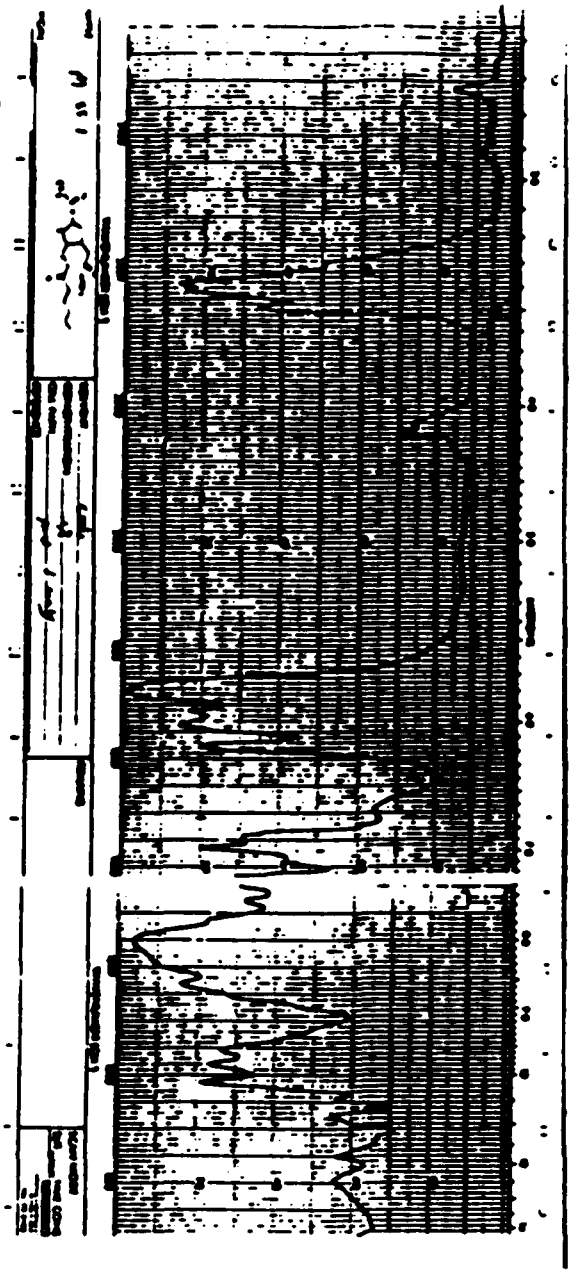
IR of 11

Appendix 2.4



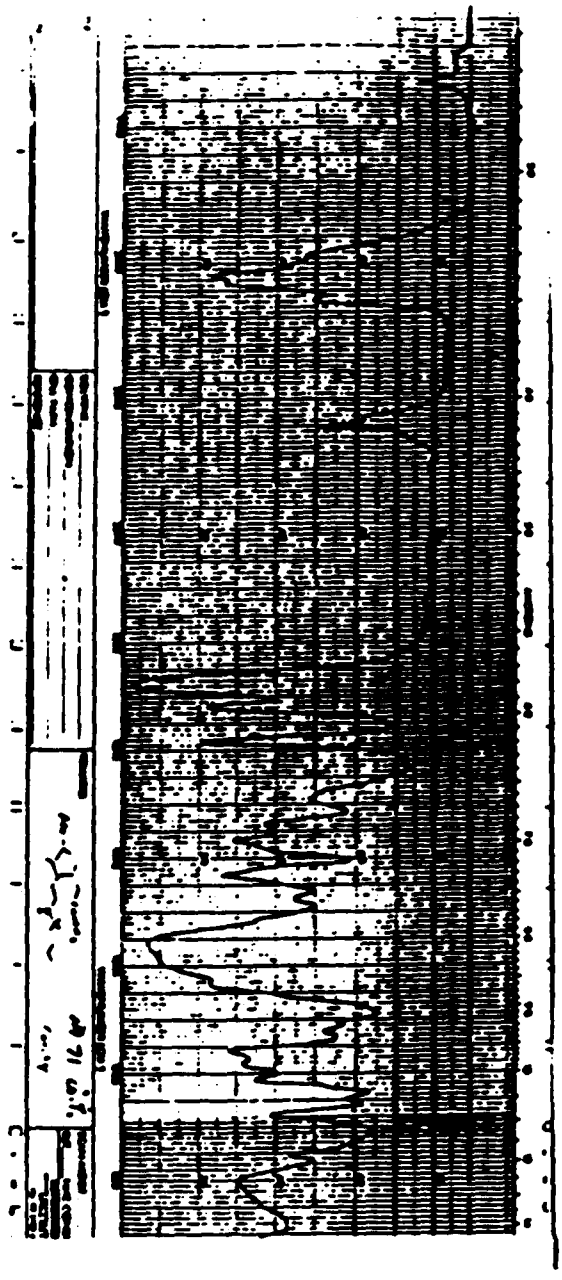
IR of L3

Appendix 2.5

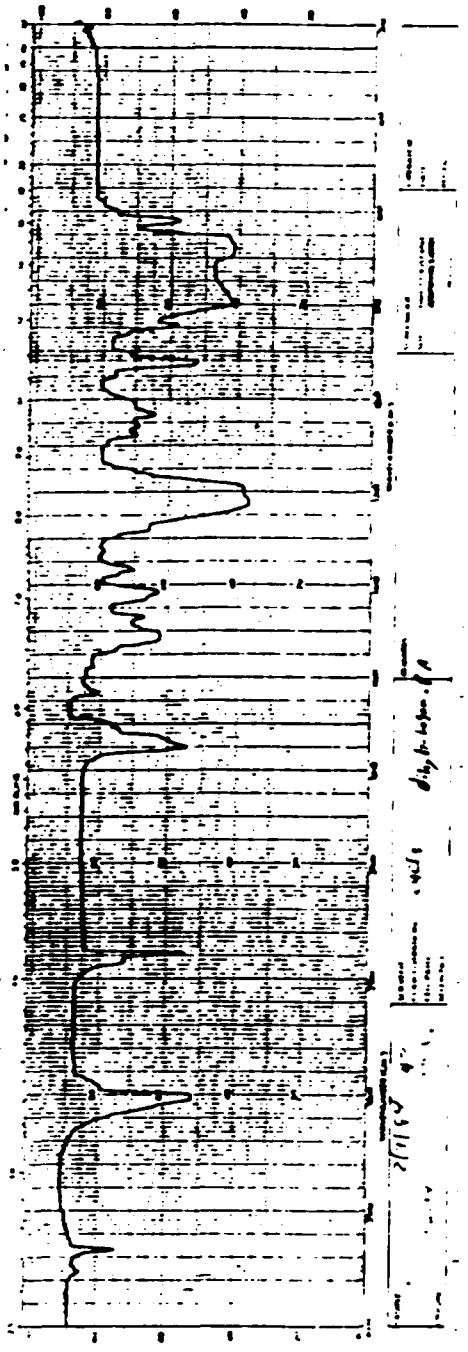


IR of 2

Appendix 2.8

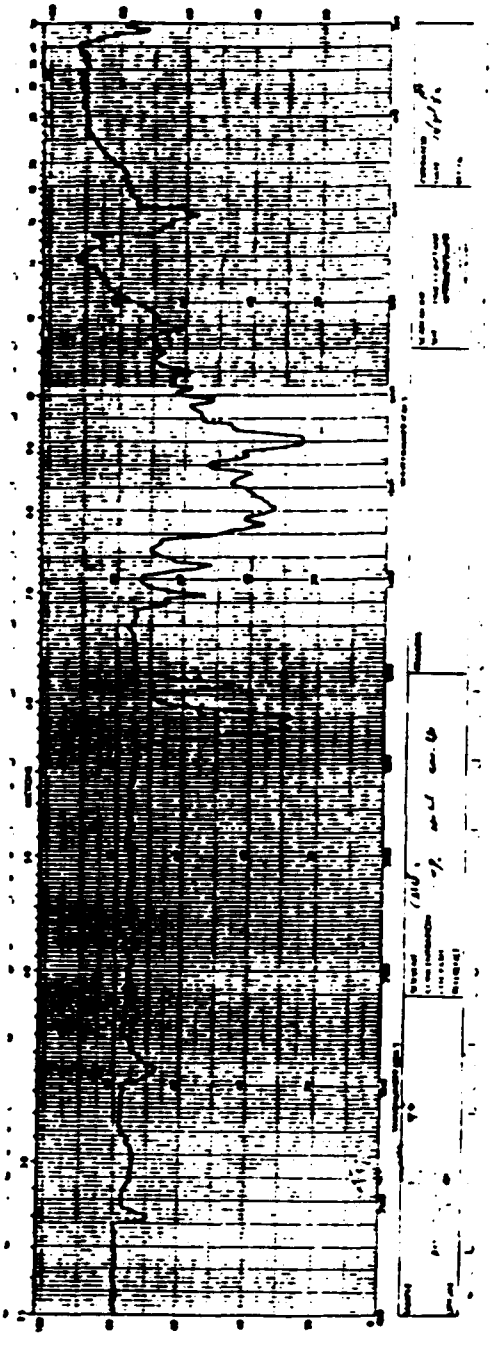


IR of 22



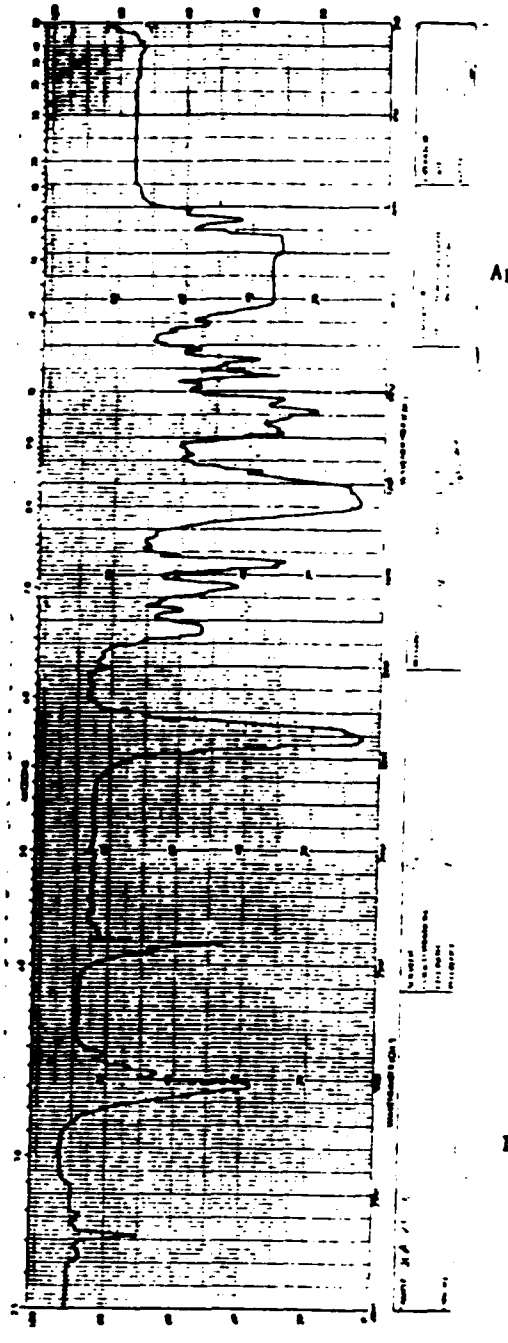
Appendix 2.7

IR of 3



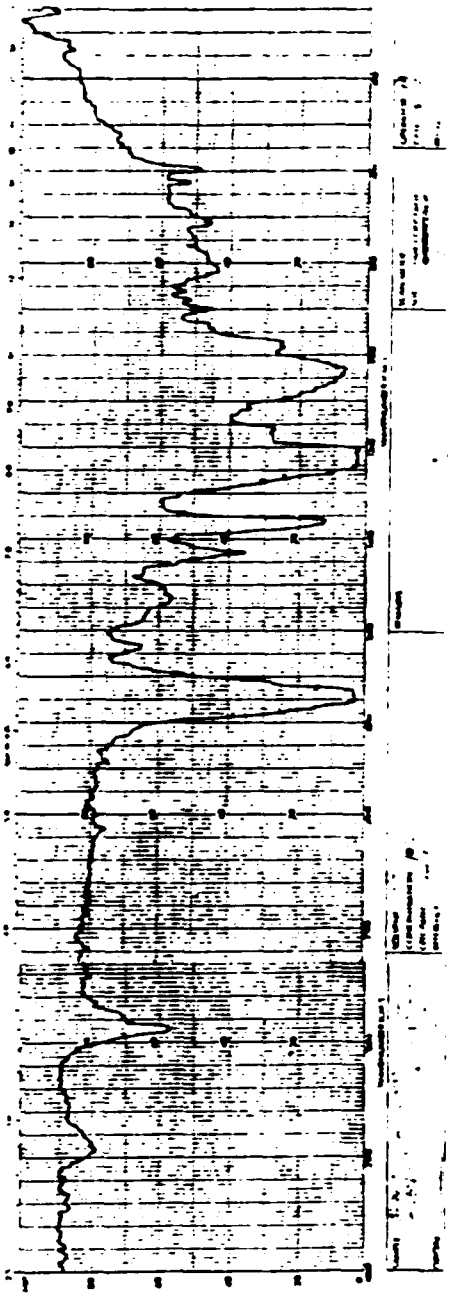
Appendix 2.8

IR of 7



Appendix 2.9

IR of 15



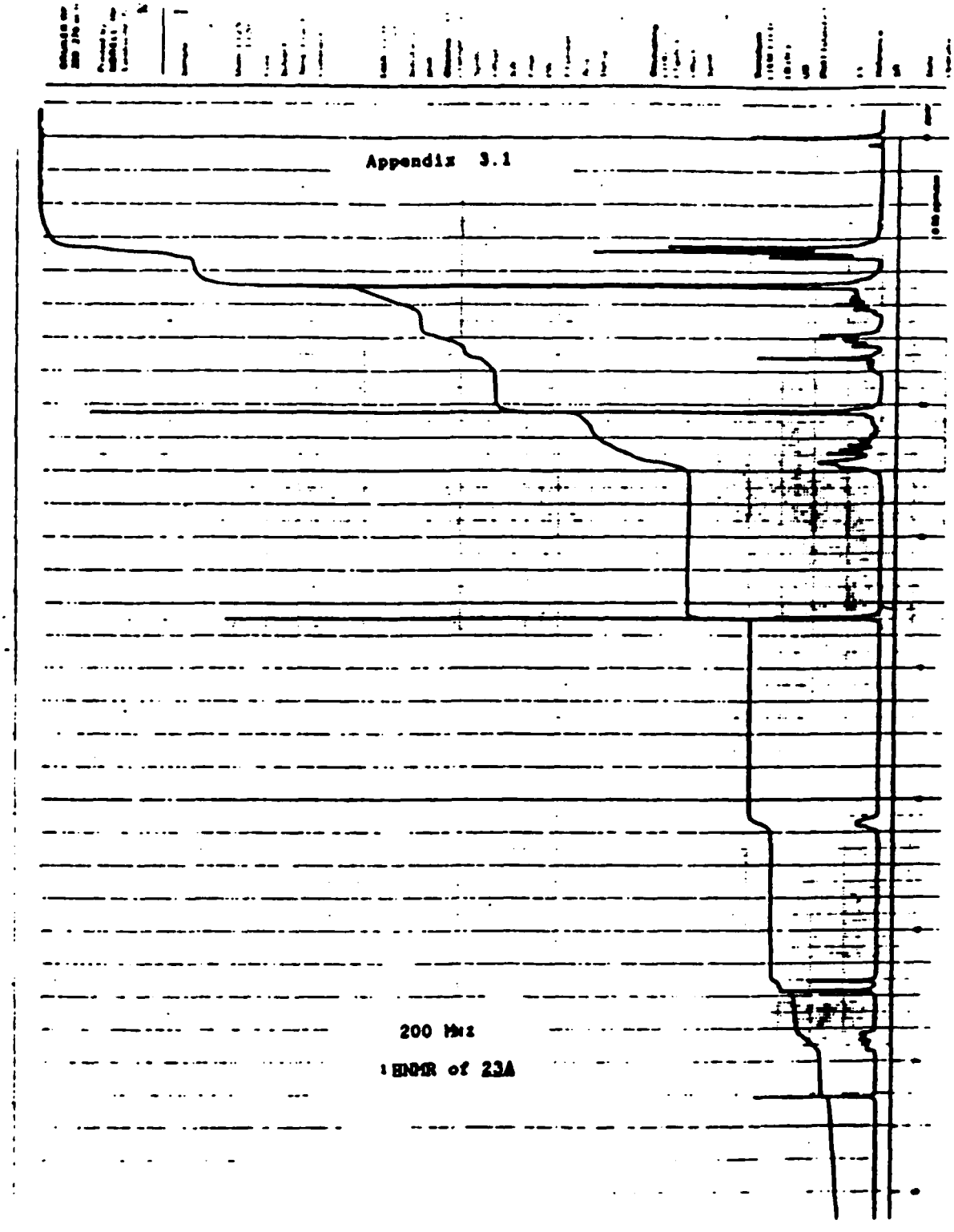
Appendix 2.10

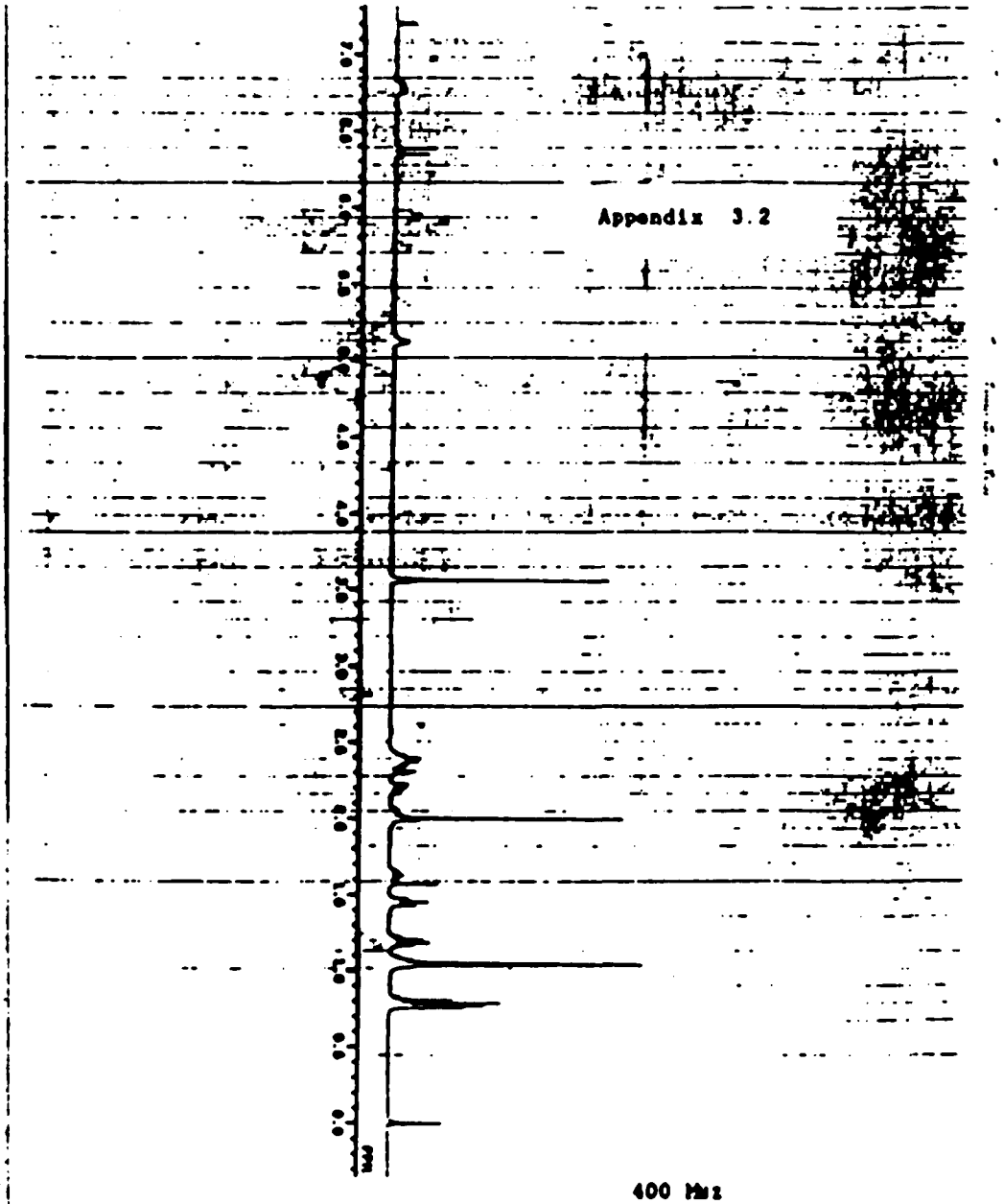
IR of 16

APPENDIX 3

^{1}HNMR SPECTRA OF 23A

(major isomer)

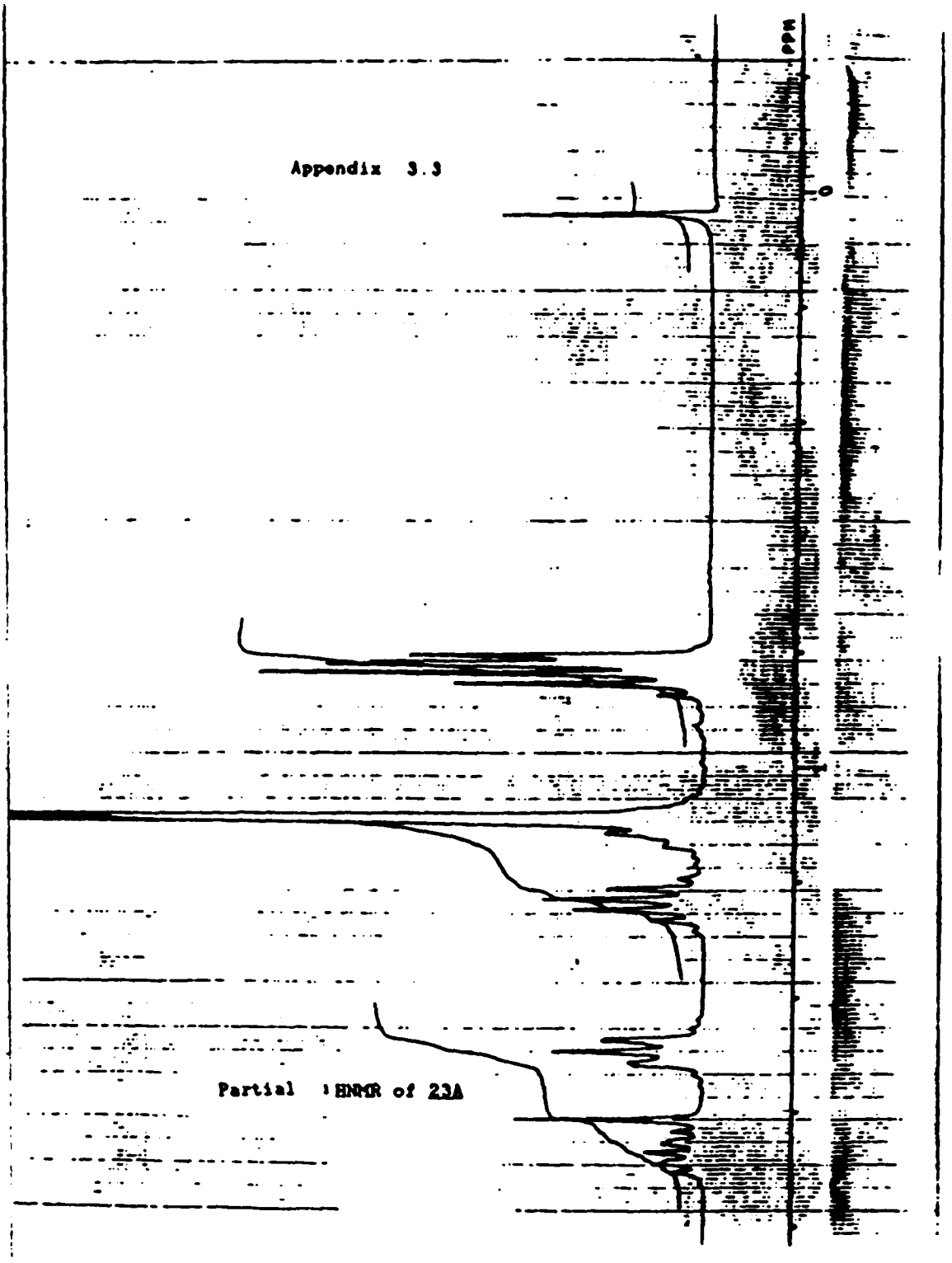

Appendix 3.1
200 MHz
¹HNMR of 23A



Appendix 3.2

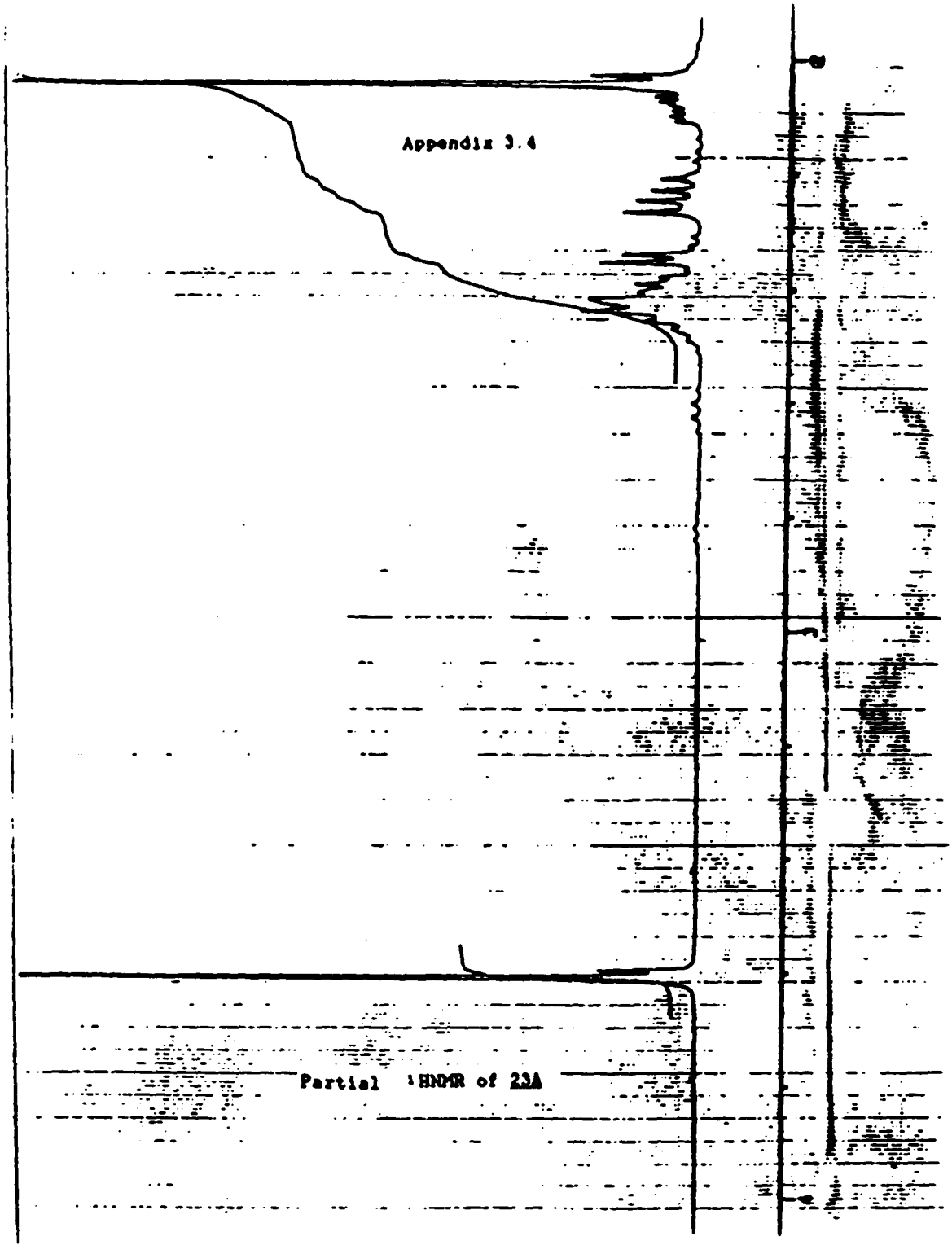
400 MHz

^{1}HNMR of 23A

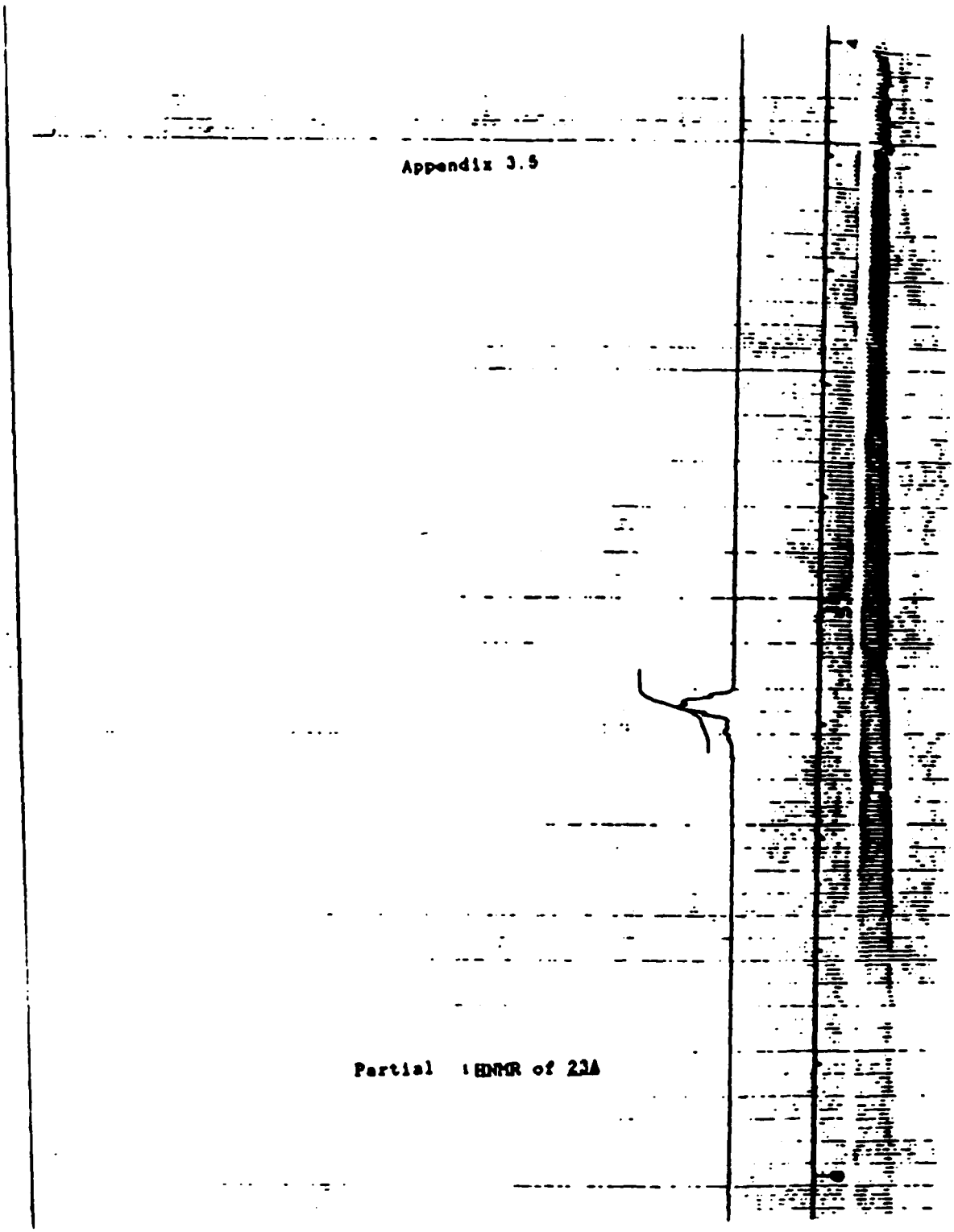


Appendix 3.3

Partial ^{1}HNMR of 23A

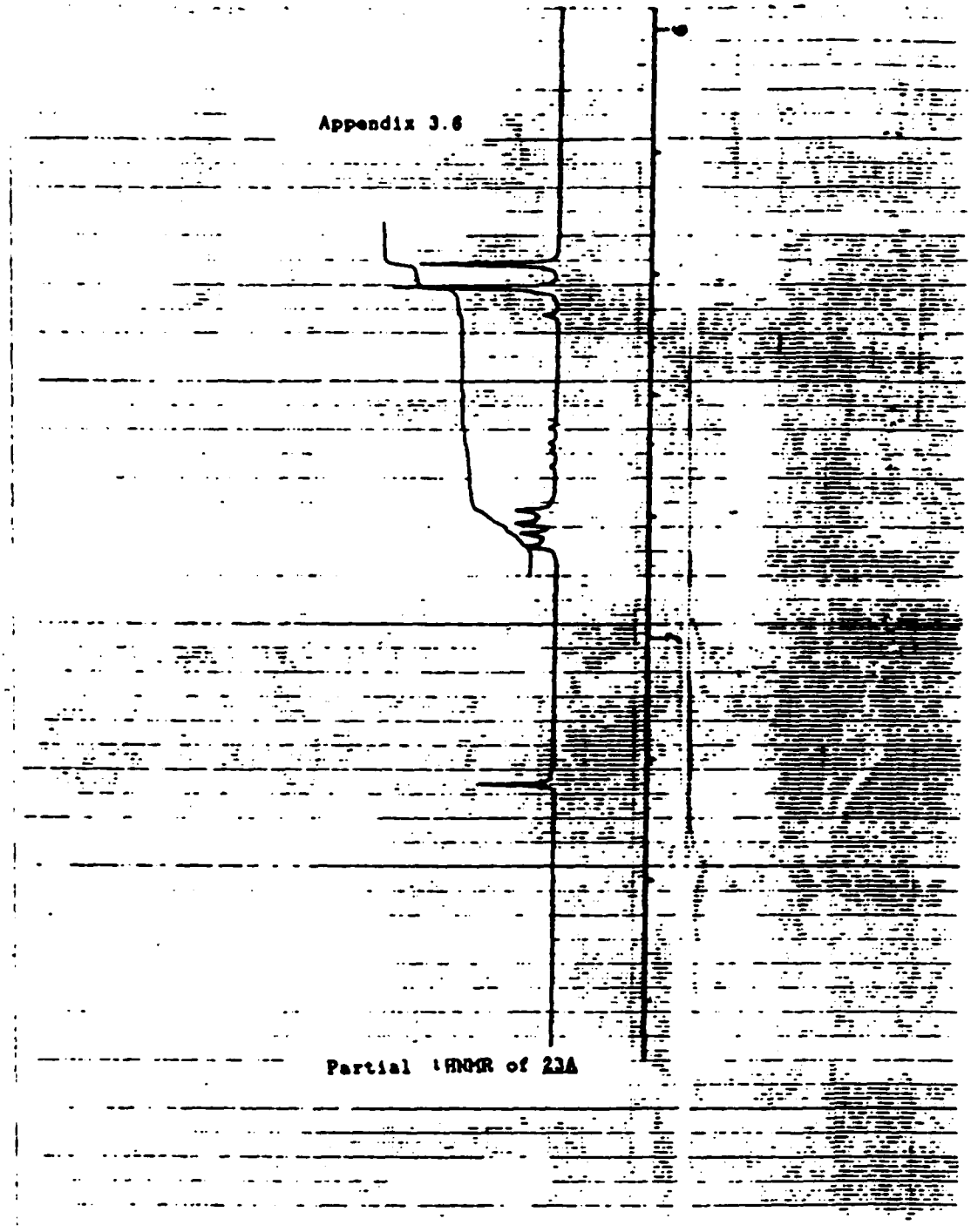

Appendix 3.4
Partial ¹HNMR of 23A

Appendix 3.5



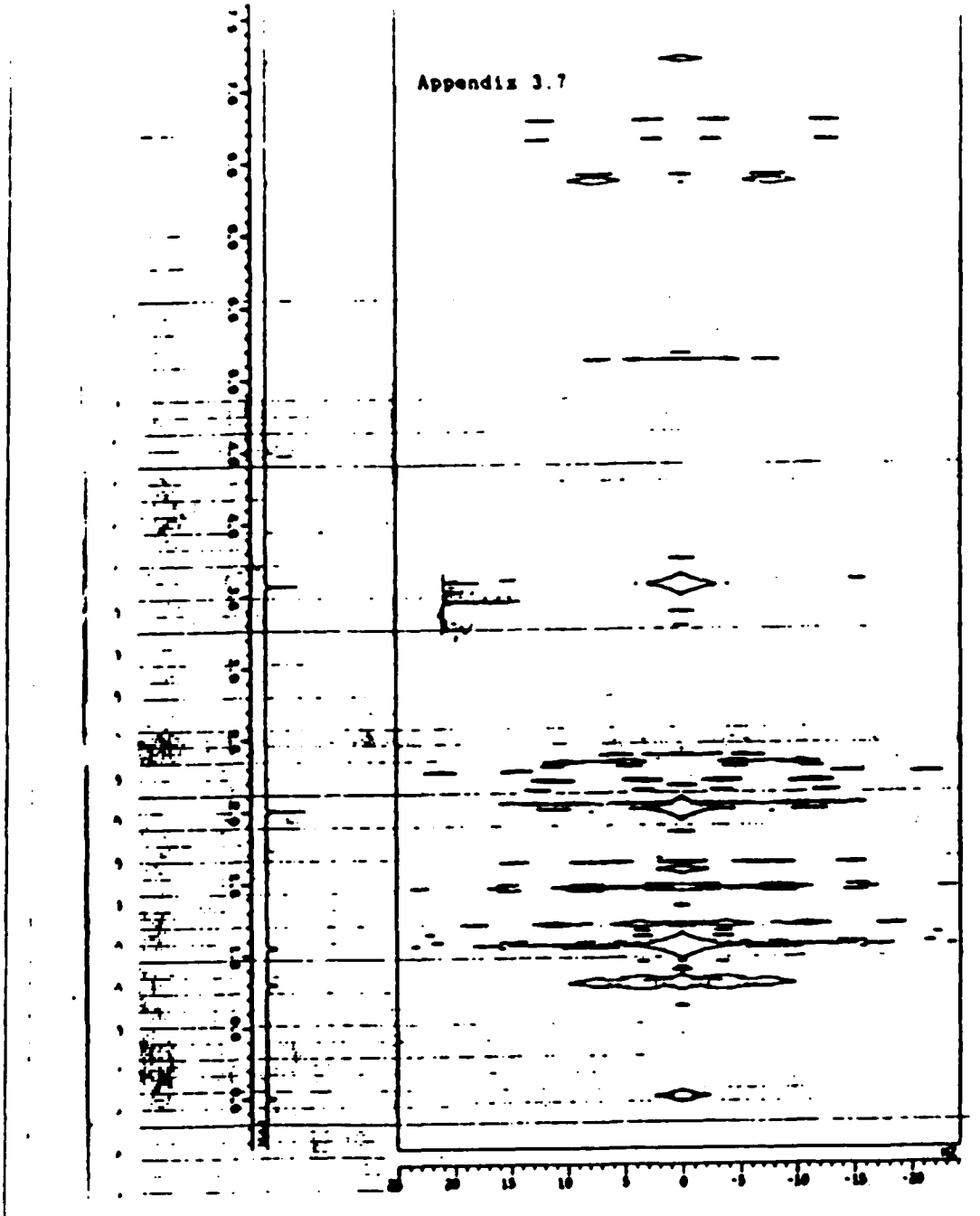
Partial ^{1}HNMR of 23A

Appendix 3.6



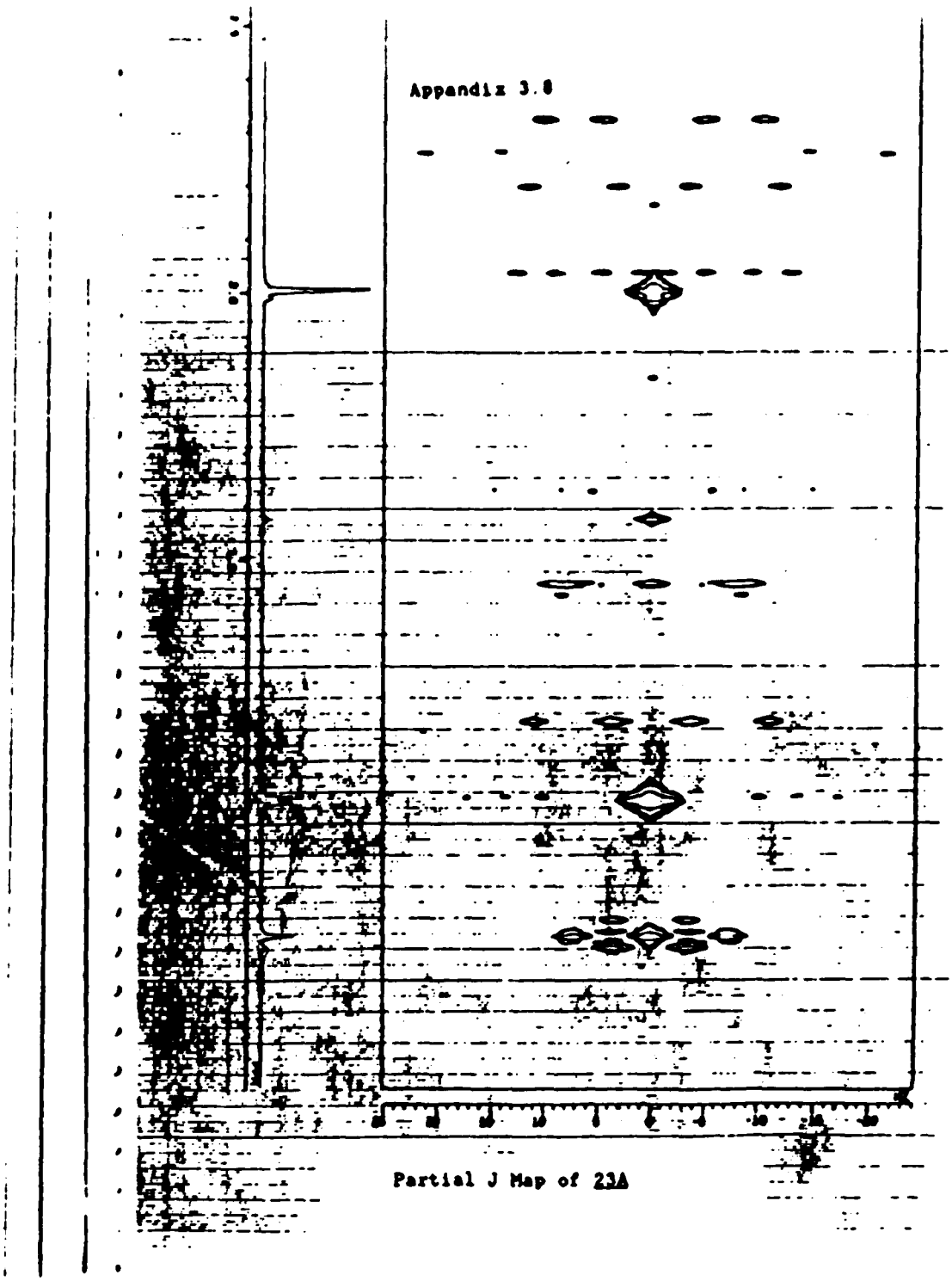
Partial ^{1}HNMR of 23A

Appendix 3.7



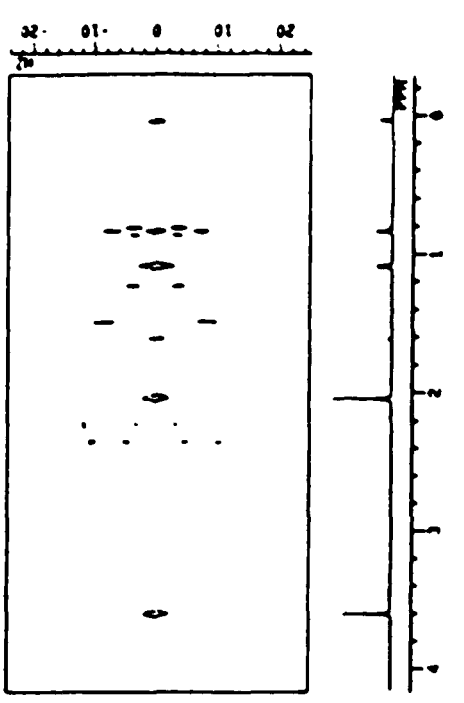
J Map of 23A

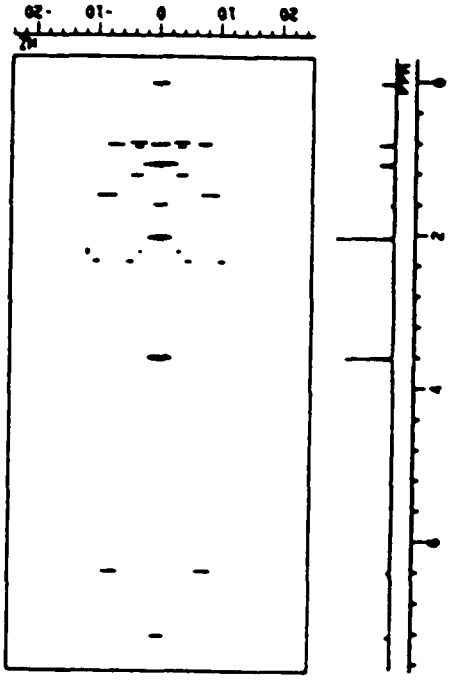
Appendix 3.8



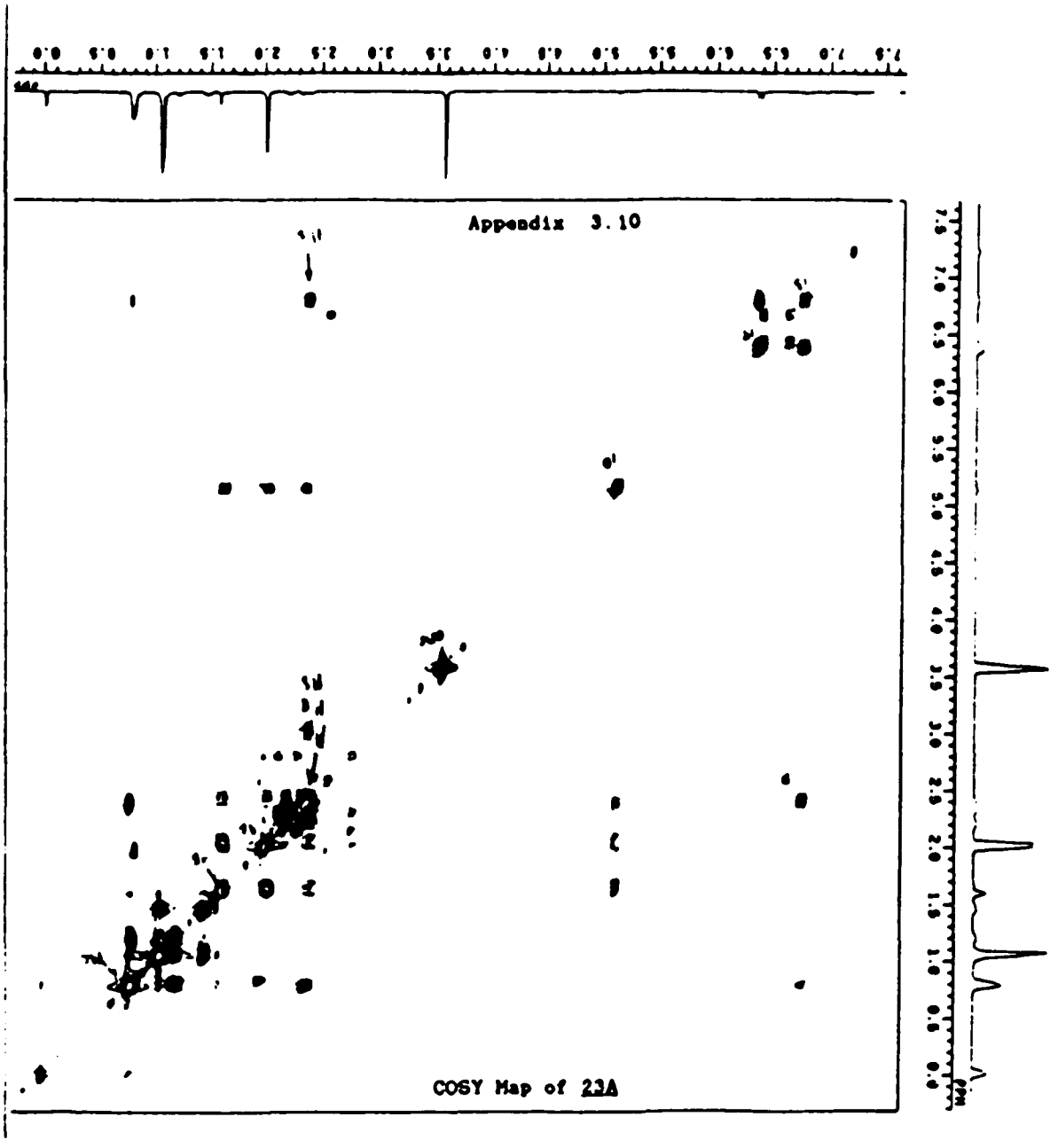
Partial J Map of 23A

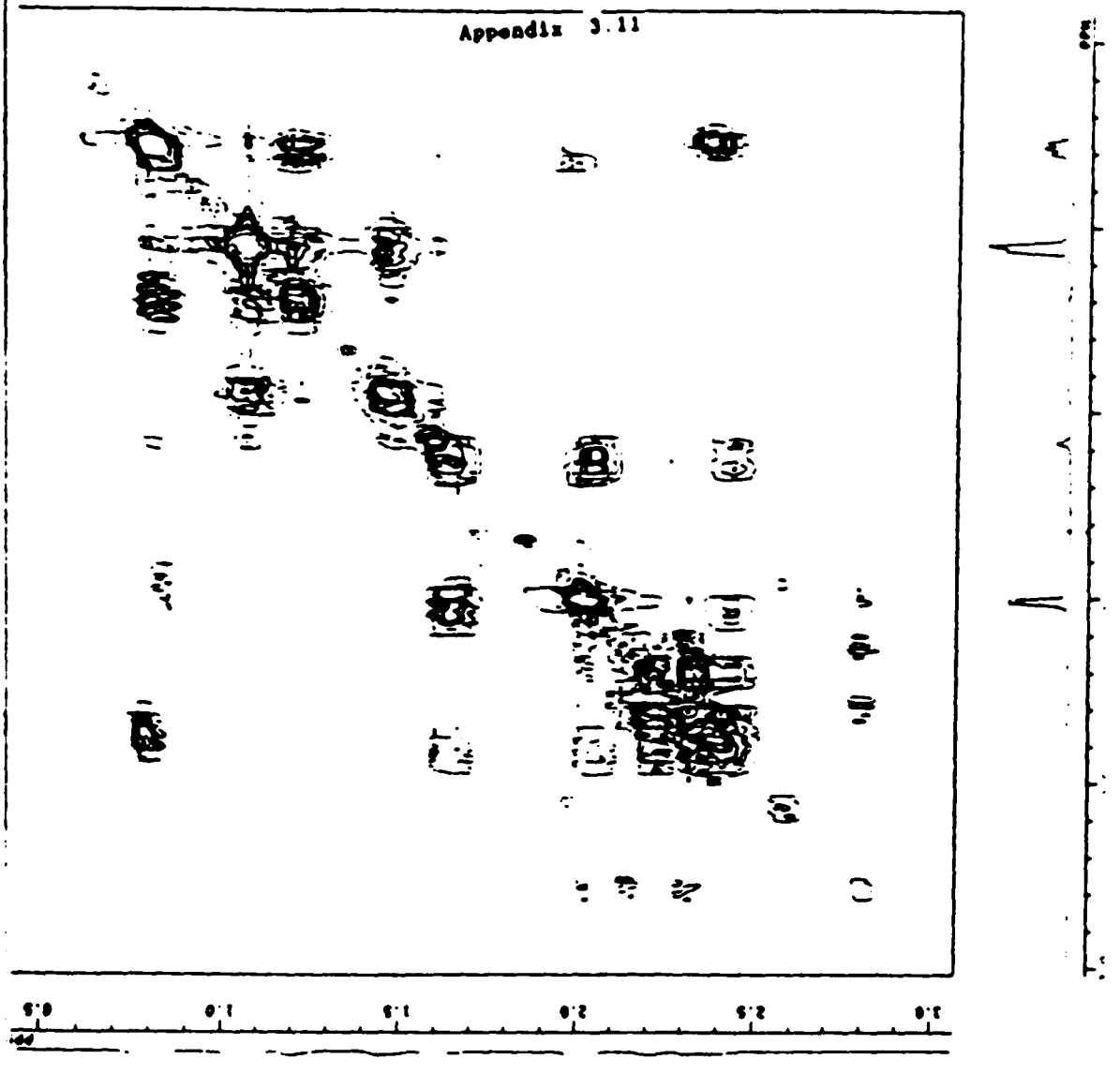
Appendix 3.9





Partial J Map of 23A


Appendix 3.10
COSY Map of 23A



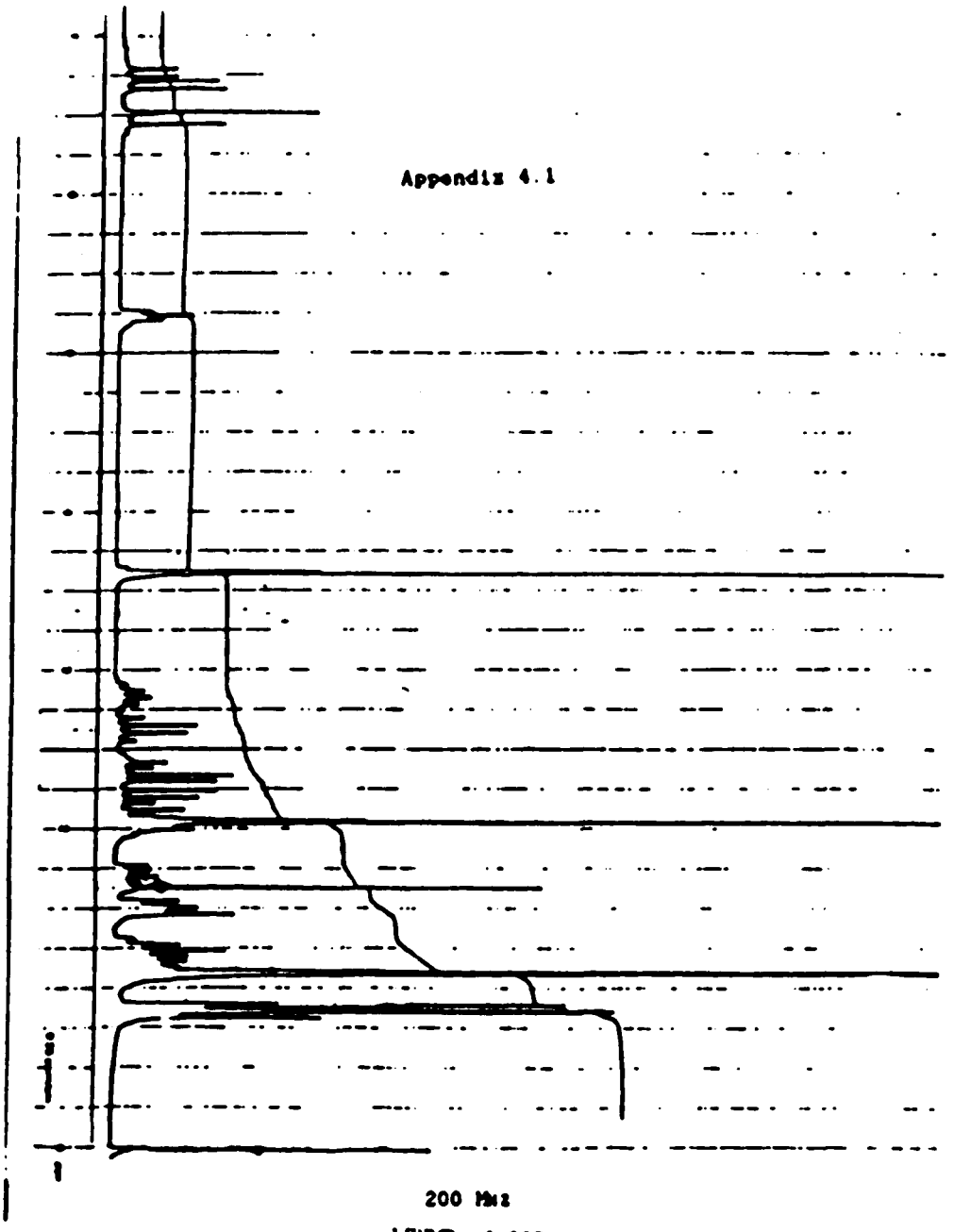
Partial COSY Map of 29A

APPENDIX 4

^{1}HNMR SPECTRA OF 23B

(minor isomer)

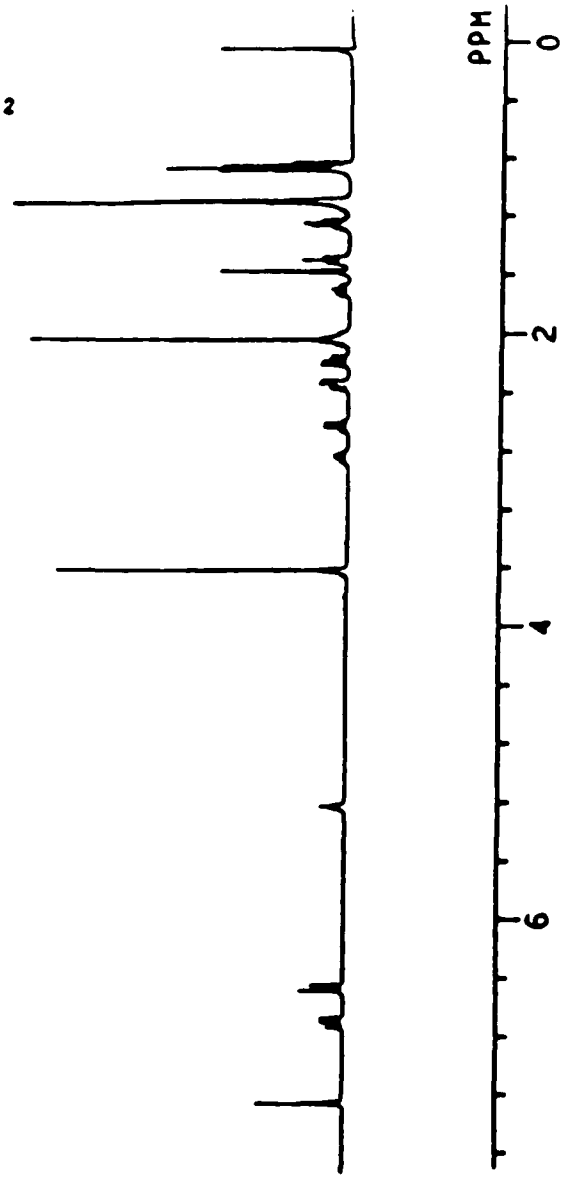
Appendix 4.1



200 MHz

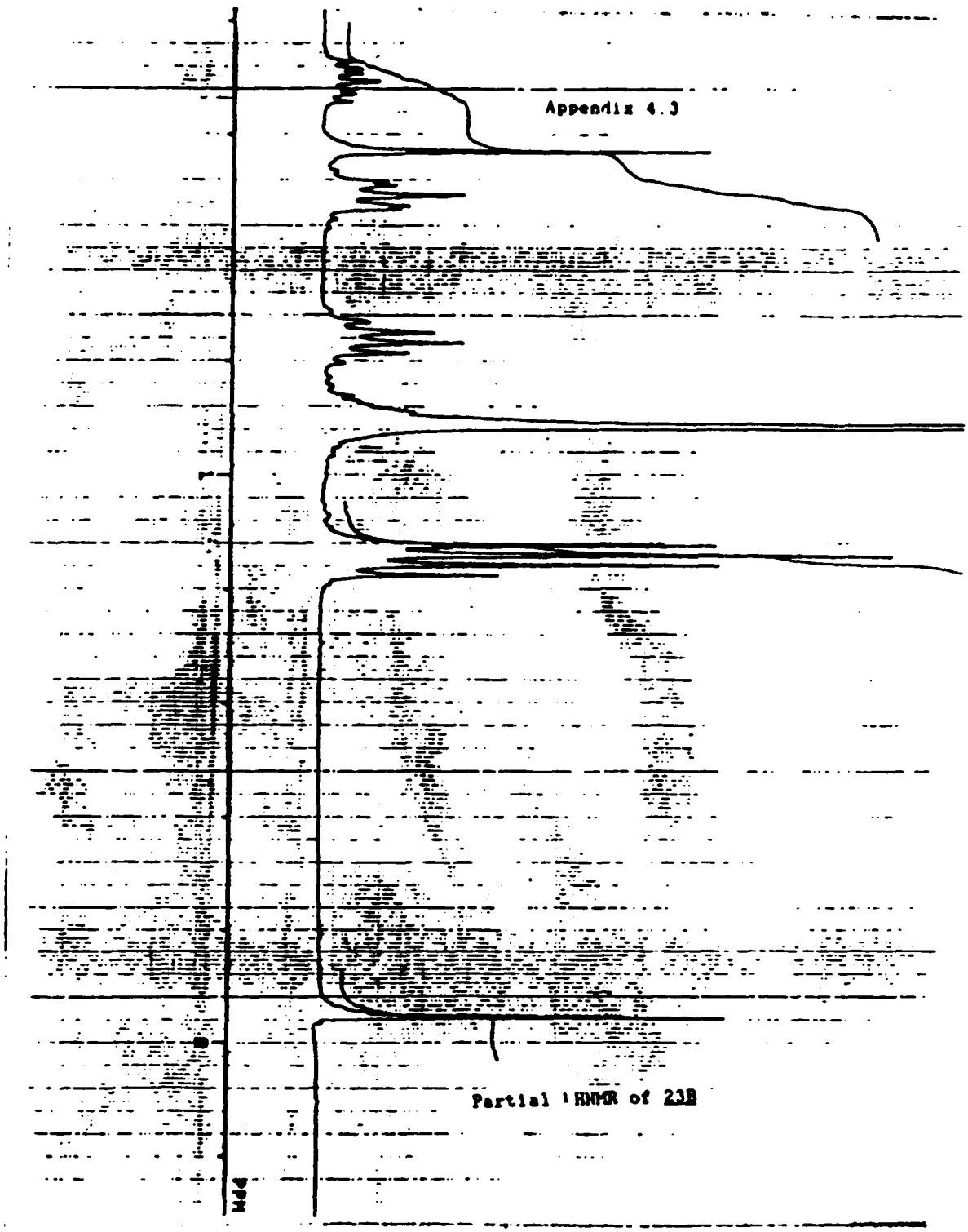
^{1}HNMR of 23B

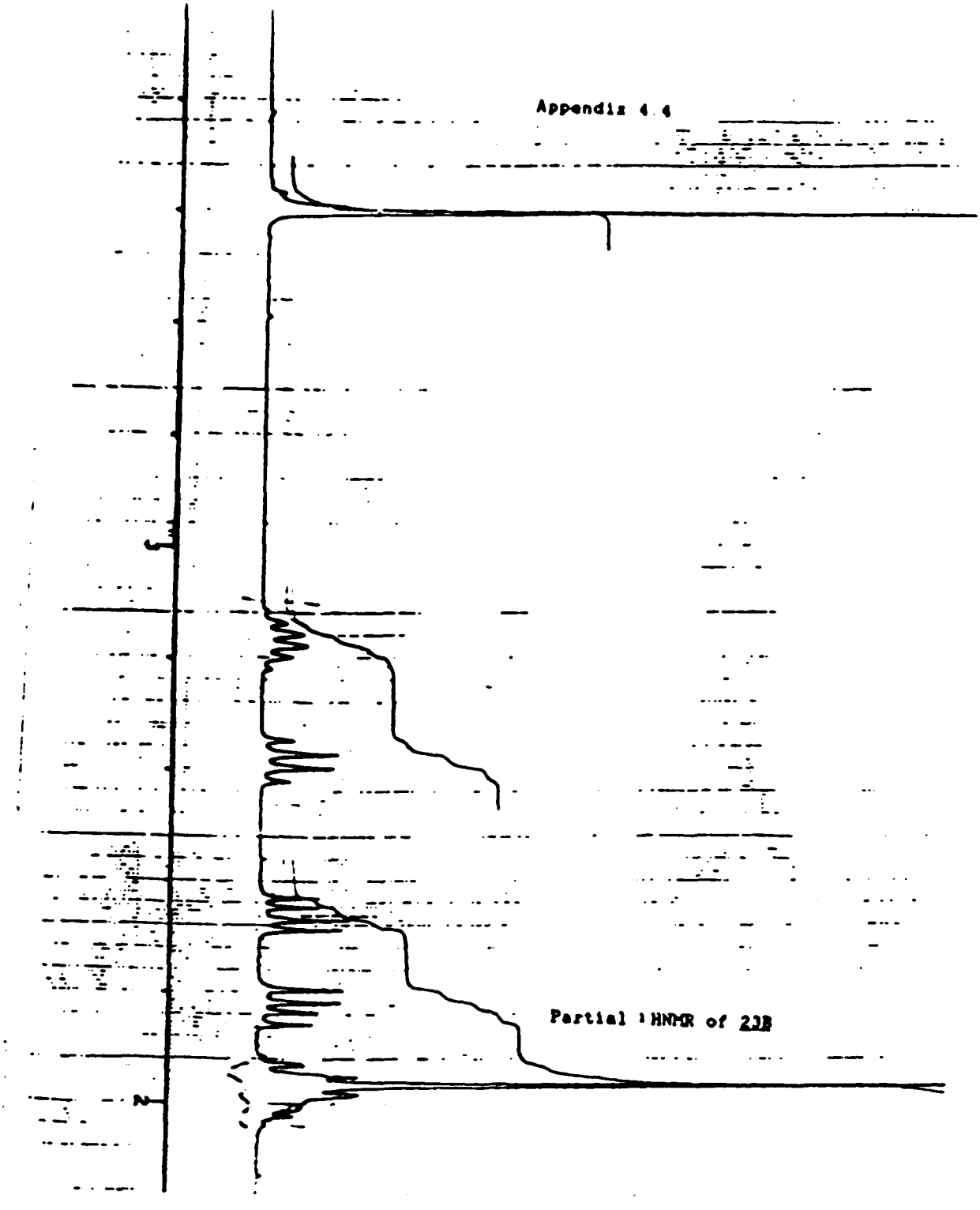
Appendix 4.2



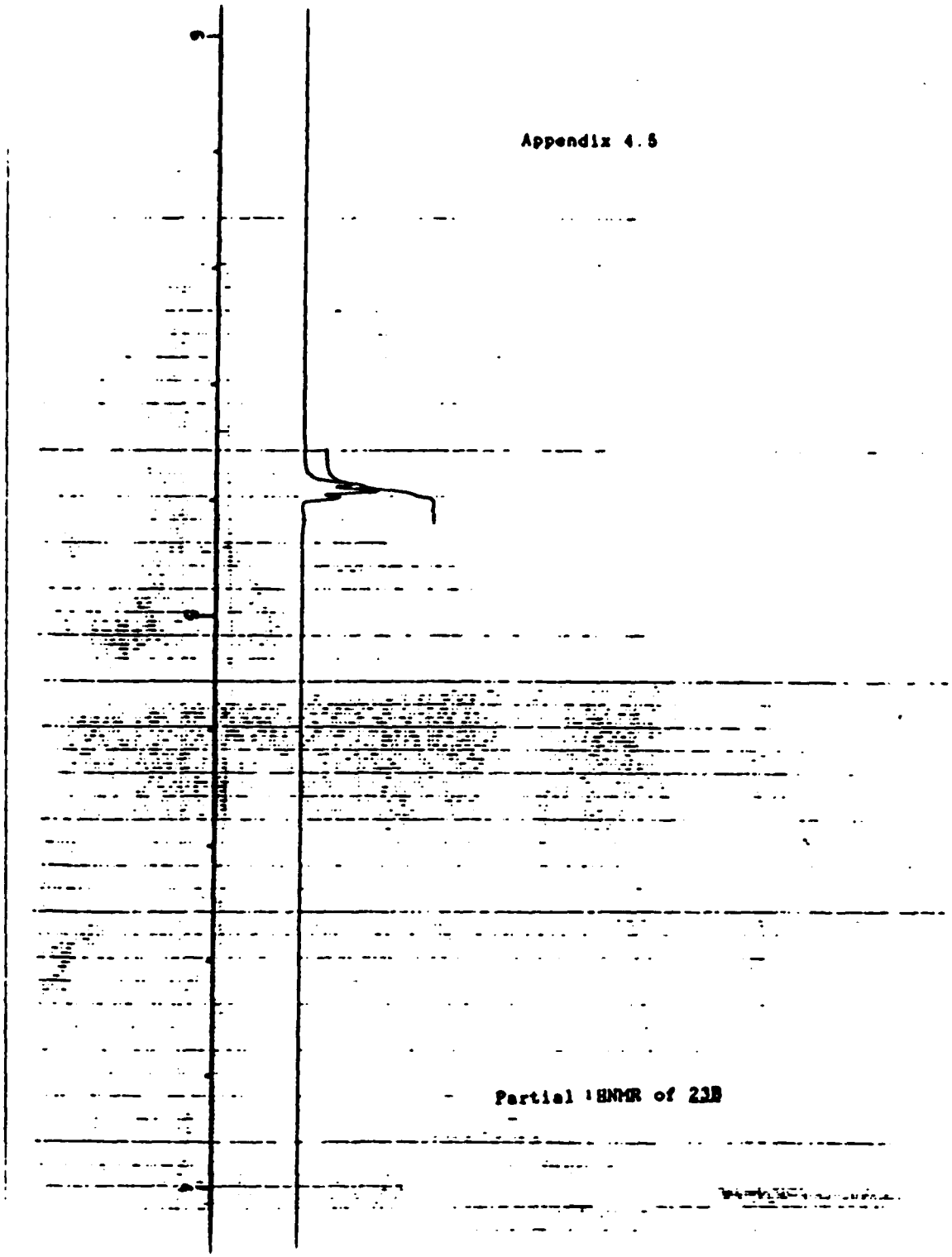
400 MHz

^{1}HNMR of 23B


Appendix 4.3
Partial ¹HNMR of 23B

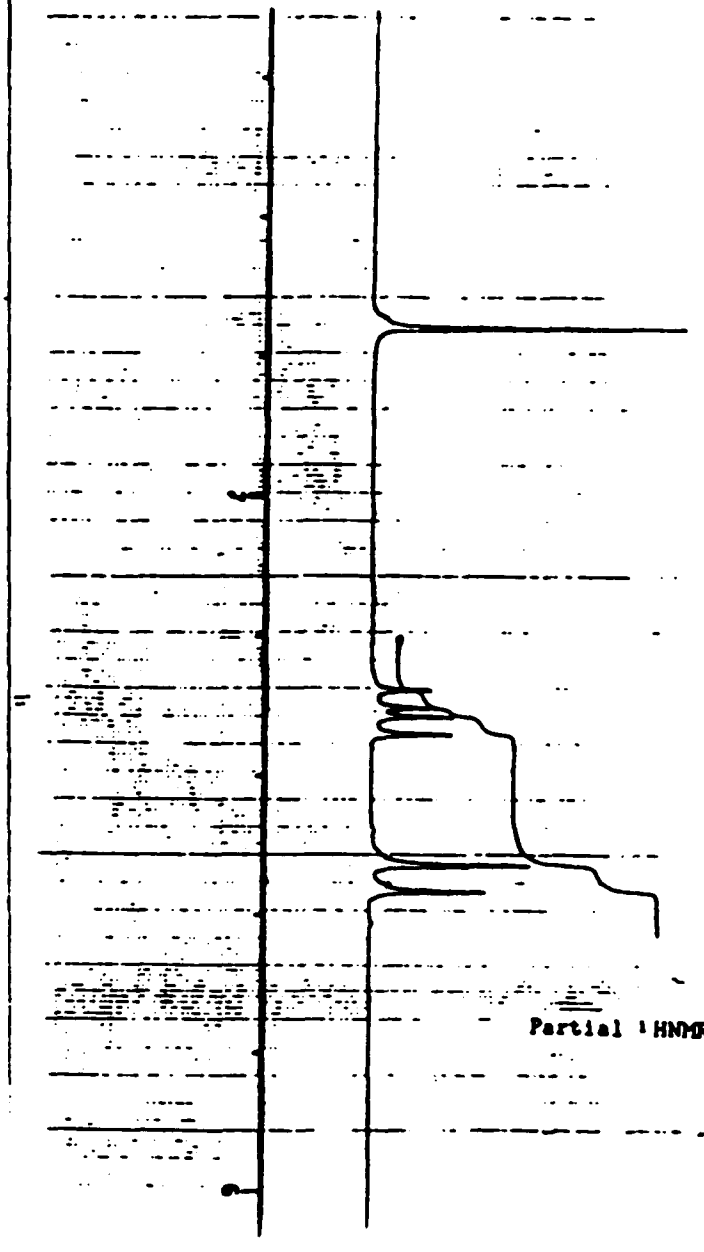

Appendix 4.4
Partial ¹HNMR of 23B

Appendix 4.5

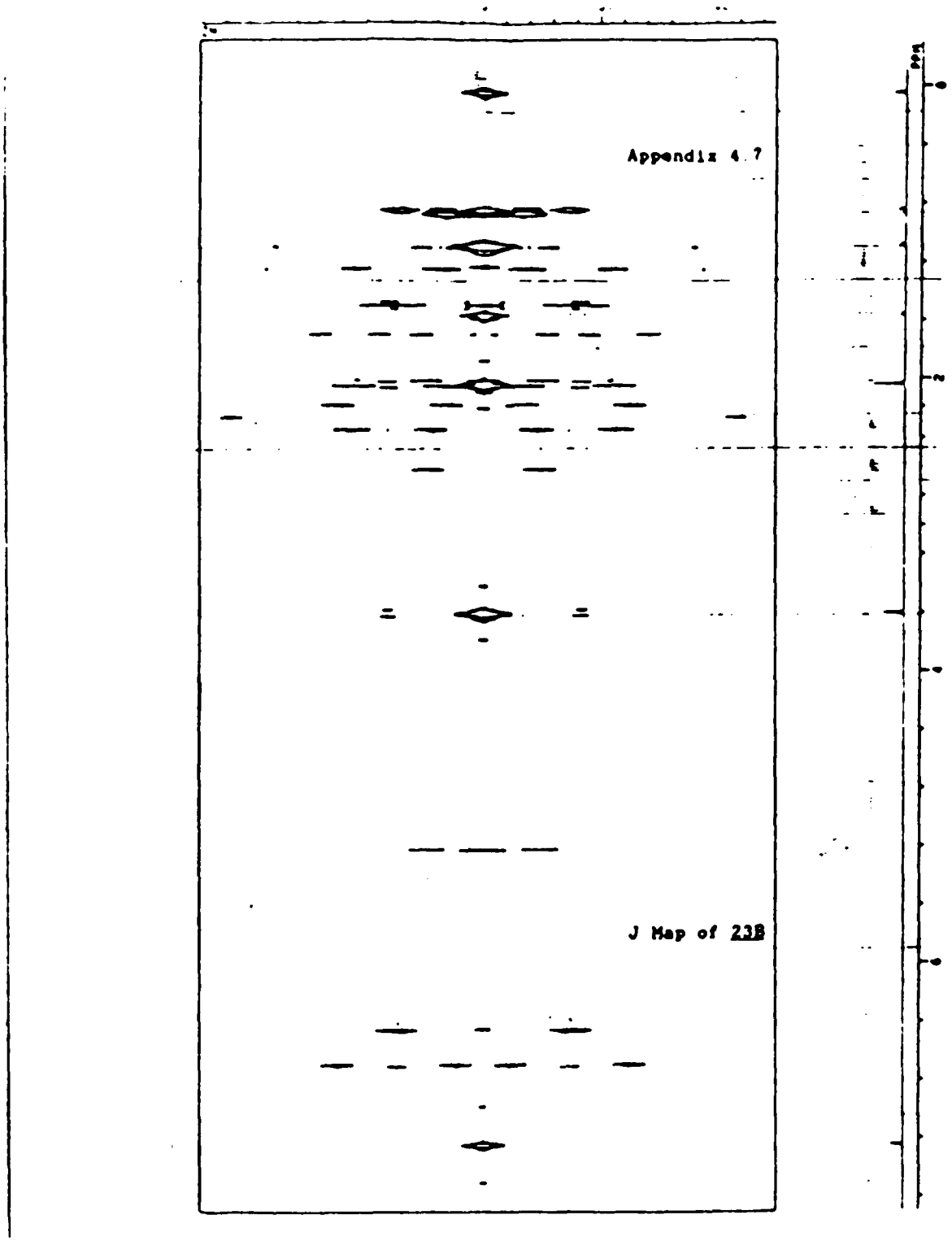


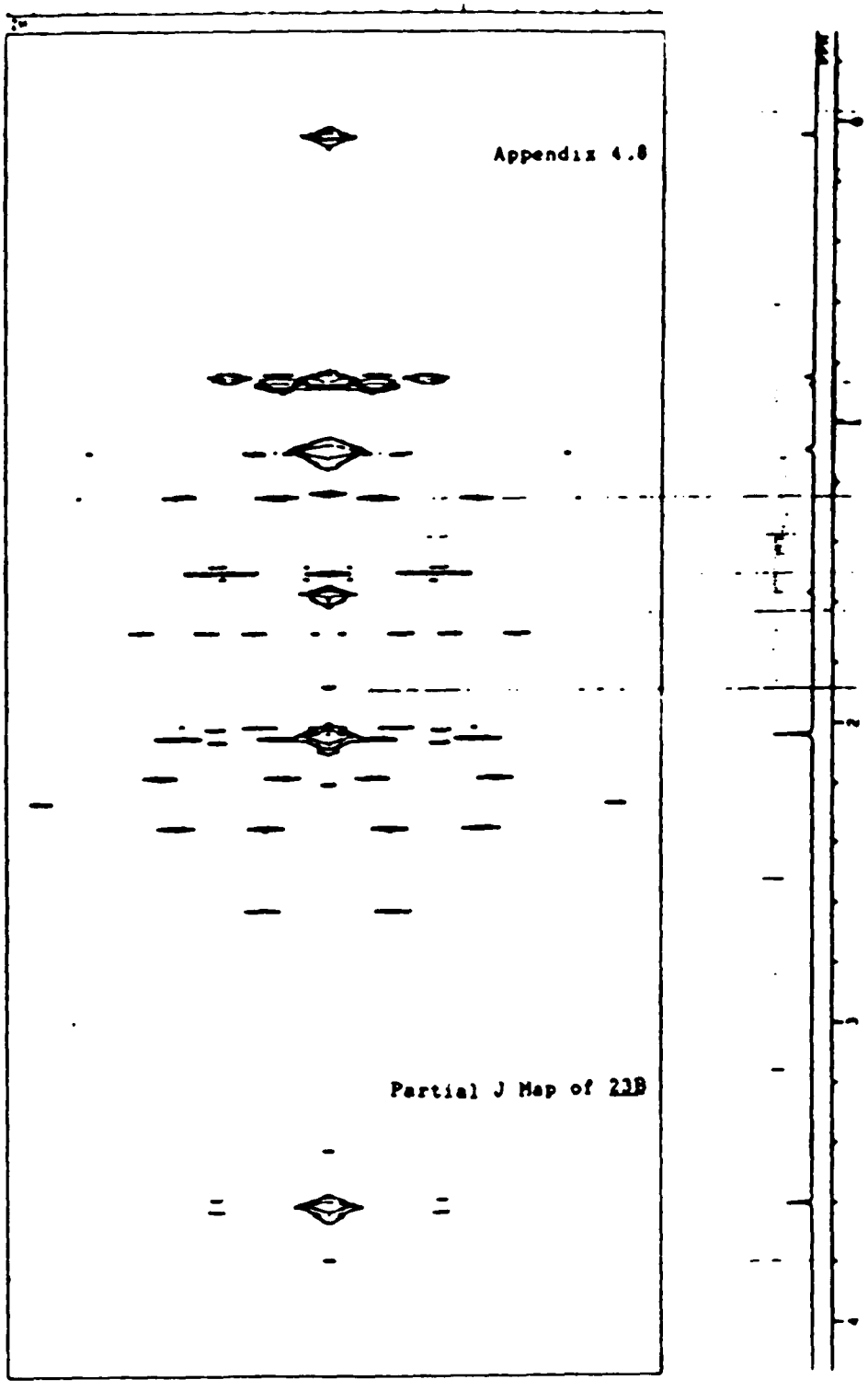
Partial ^{1}HNMR of 23B

Appendix 4.6

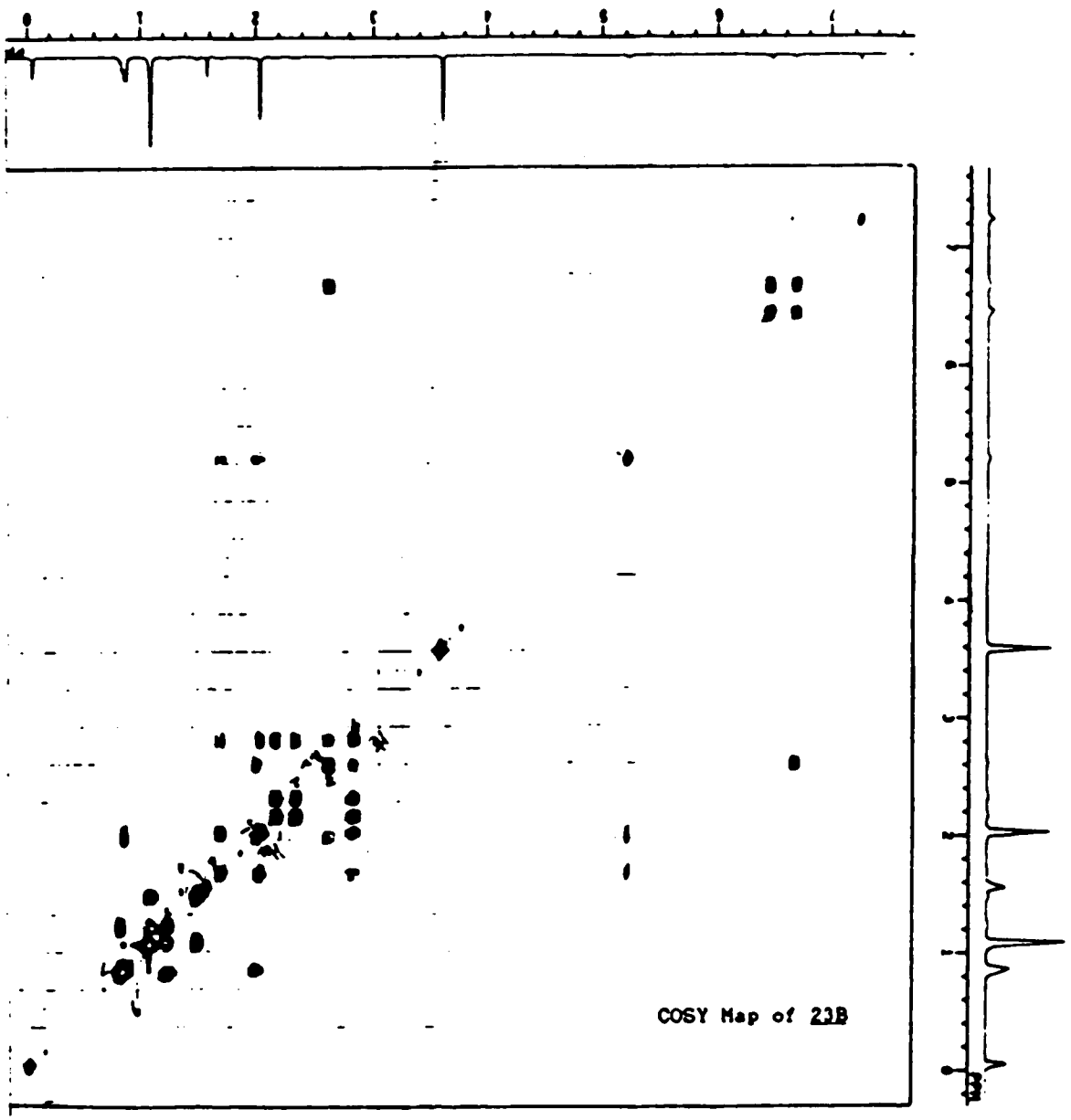


Partial ^{1}HNMR of 23B

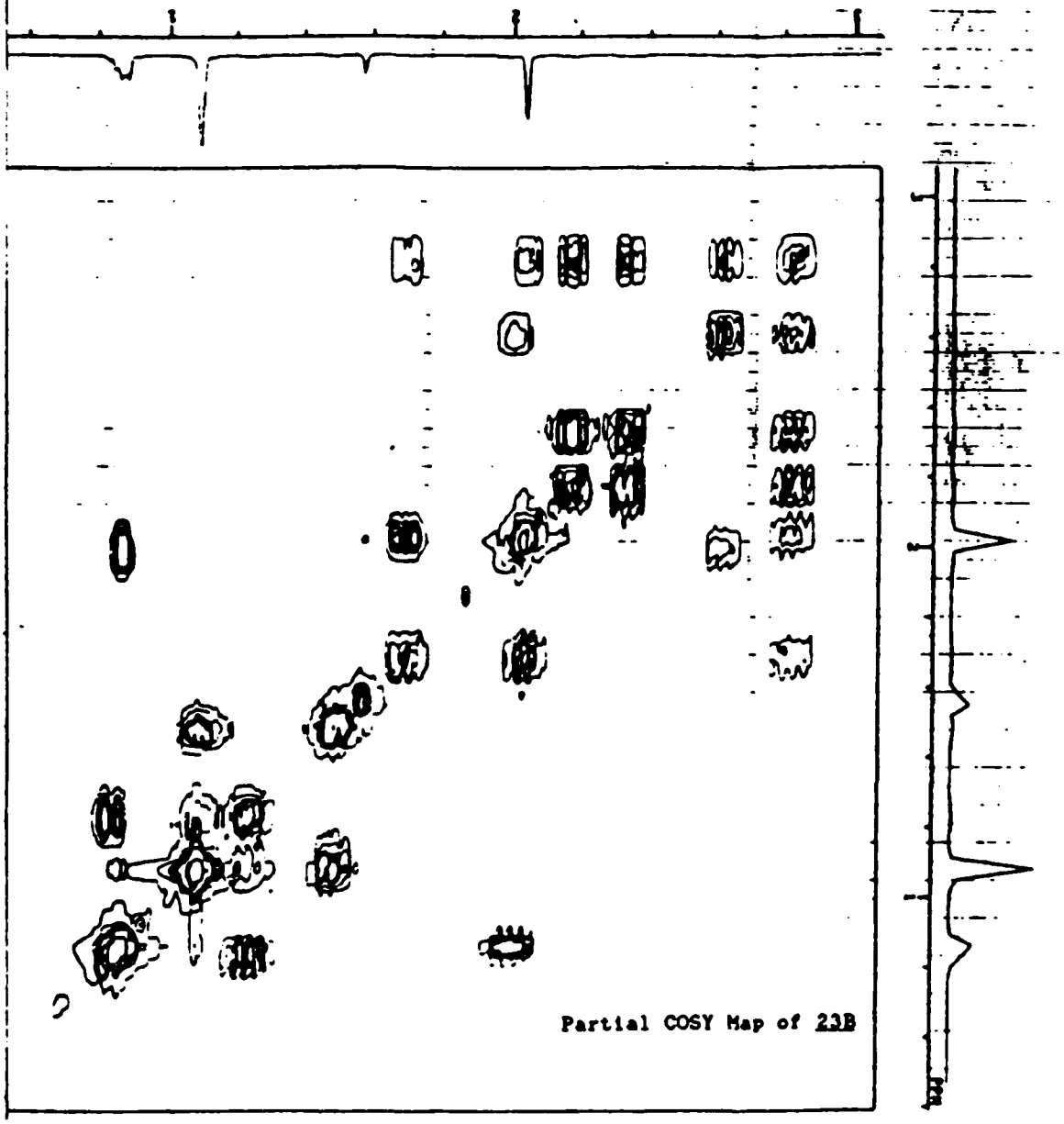

Appendix 4.7
J Map of 23B


Appendix 4.8
Partial J Map of 23B

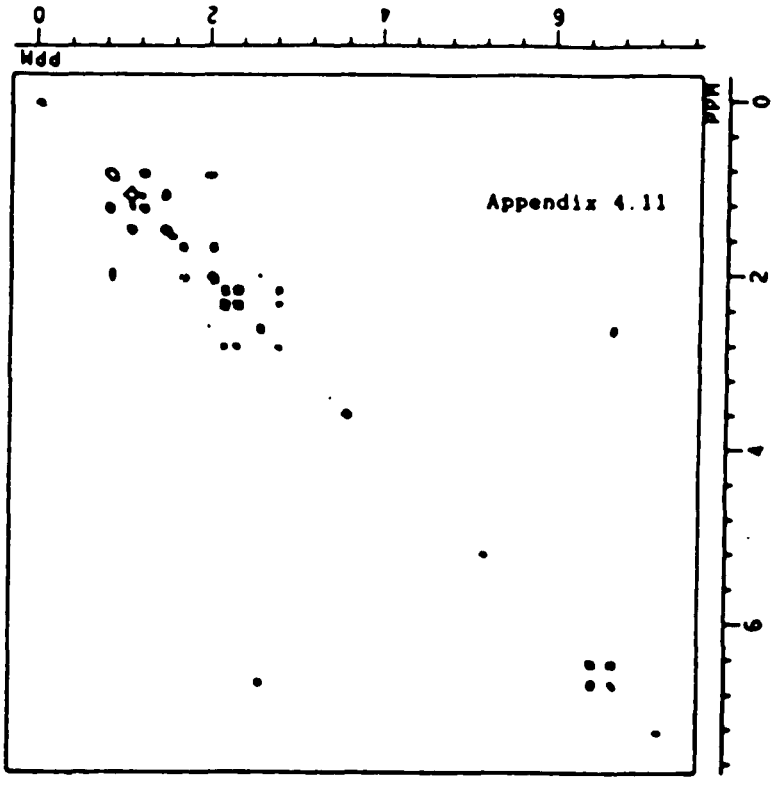
Appendix 4.9

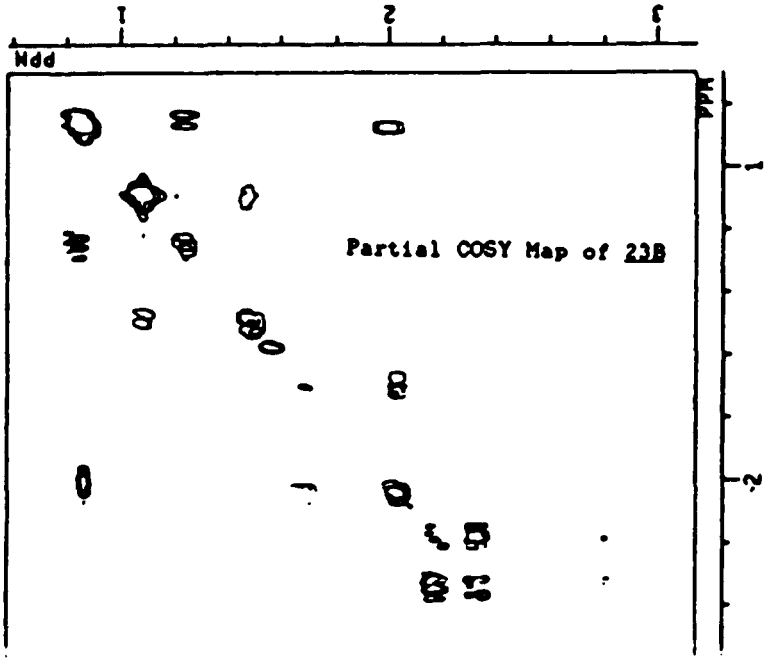


Appendix 4.10



Partial COSY Map of 23B


Appendix 4.11


Partial COSY Map of 23B

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